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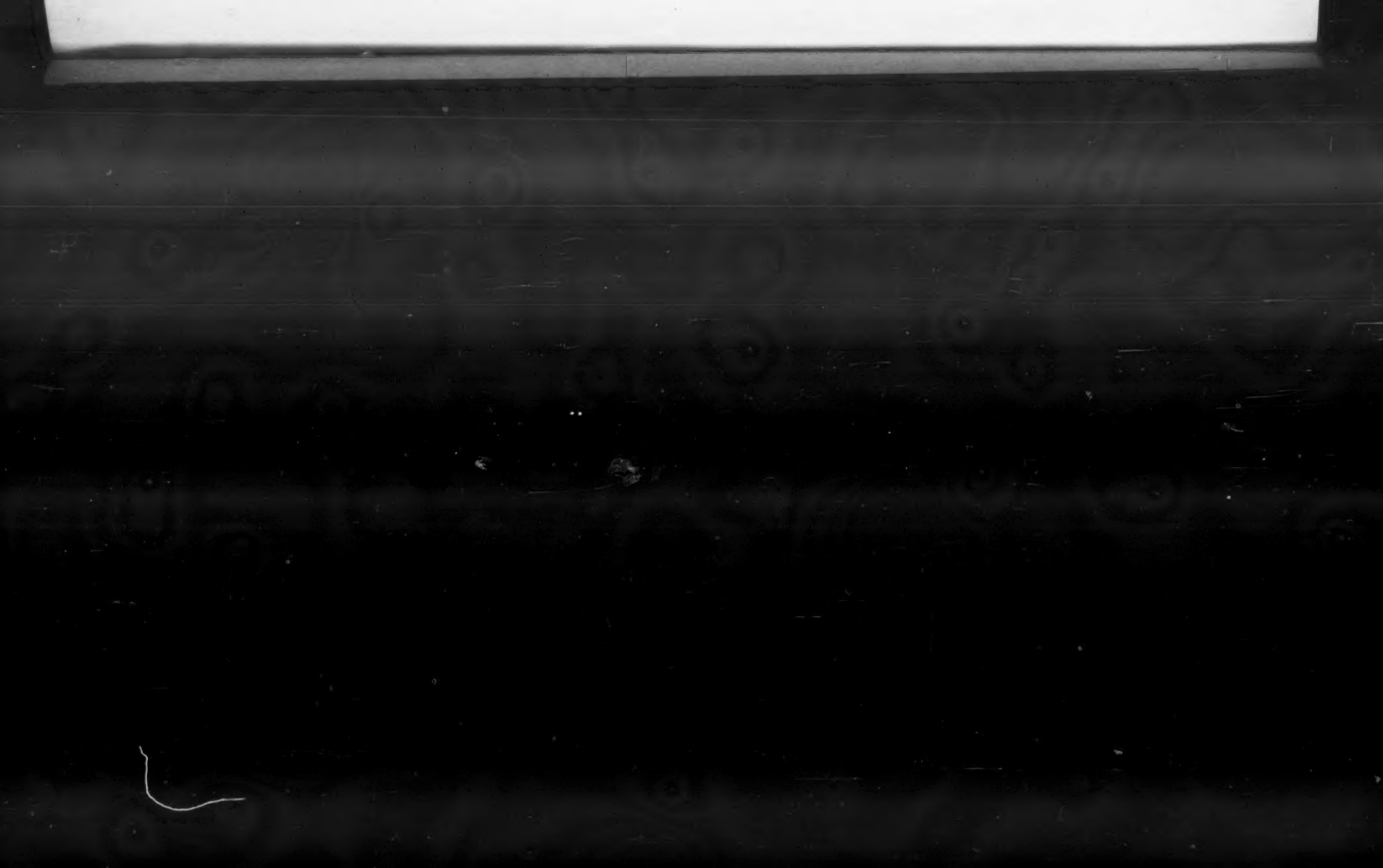

The American Heart Journal

VOL. IV AUGUST, 1929 No. 6

Original Communications

SOME UNSOLVED PROBLEMS CONNECTED WITH ACUTE OBSTRUCTION OF THE CORONARY ARTERY*

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THE purpose of this paper is to present in outline certain features of acute occlusion of the coronary artery concerning which there is still some obscurity. The hope is that a frank statement of these problems may stimulate clinicians, pathologists, and experimental workers to study and solve them. It is to be noted that acute occlusion of the artery is the only topic under consideration. Chronic, i.e., slowly progressive occlusion is not sharply demarcated from the acute process, but its features are of somewhat different character and may well be separately considered, at least for the present.

RELATION TO INFECTION

Occasionally the occlusion is by an embolus. Generally, however, a thrombus is the cause. In practically all the thrombotic cases in which autopsy has been performed a chronic change in the vessel wall is mentioned—atheromatosis, especially patchy atheromatosis; roughening; calcareous plaques; narrowing, especially at a point of bifurcation; arteriosclerosis. That this chronic change is the sole cause is not clear.

What may be the influence of physical or chemical changes in the blood, or of an altered number of blood platelets is unsettled. Does a slower or feebler blood current have any effect? Particularly, what is the influence of infection? Several writers have called attention to the frequency with which acute coronary occlusion has been preceded by general infectious processes or by a local infection in another part of the body. They suggest a secondary inflammation of the wall of the coronary artery as a factor that may favor thrombosis. In connection with rheumatism and other infections acute changes in the walls of arteries have been noted. It is suggestive as fitting in with clinical experience that von Glahn and Pappenheimer find that the arteritis due to pyogenic infections may cause thrombosis while that

*Read at the Meeting of the Association of American Physicians, Atlantic City, May 7, 1929

accompanying rheumatism seems not to show this tendency. Boyd's studies are worthy of note. He shows acute mural changes in the coronary artery in addition to the chronic, and believes there is definite evidence of an inflammatory basis for coronary occlusion.

Here, then, is a problem: to discover what factors aside from the chronic change in the vessel wall determine the formation of a thrombus; especially, to what extent do focal or general infections play a part in this process? In what proportion of cases does the wall of the coronary artery show acute as well as chronic changes that might favor thrombotic occlusion? Do certain infections favor thrombosis while others do not? Why is it that syphilis that so often works damage to the aorta and the mouths of the coronaries plays such a minor part in the tragedy of acute coronary occlusion?

EMBOLIC PHENOMENA

Secondary embolic manifestations may occur soon or late after myocardial infarction. Some report this as a not uncommon complication. Others have seen comparatively few instances. The explanation offered for the occurrence is that from the intracardiac thrombus that so commonly forms over the infarcted area fragments are detached that, as emboli, obstruct peripheral vessels. There are clinical and post-mortem reports of coronary occlusion with emboli in the arteries of the brain, spleen, mesentery, retina, and extremities. If the intracardiac thrombus is in the right heart the emboli may produce pulmonary infarction.

Granting that the origin of the emboli in the intracardiac thrombus is the probable explanation, the question may yet be raised whether there may not be another origin, at least in some instances. If an infectious process has produced coronary arteritis may not this same process produce as well a similar change in the wall of some other artery, e.g., in the brain, leg, or spleen? The weak action of the heart and the feebler blood current, results of the damage done to the myocardium, may still further favor thrombus formation.

The question then seems proper: May the supposed secondary embolic manifestations at times be due to multiple thrombi resulting from widespread acute arterial inflammation?

In this connection it may be recalled that some regard postoperative pulmonary infarction as often due to the formation of a thrombus in situ rather than to an embolus having its origin in a thrombosed vein at the seat of operation.

PHLEBITIS

There are few observations on the condition of the coronary veins in cases of this accident. Is there evidence of phlebitis or of venous thrombosis? If such changes are present, what is the effect on the heart's activity? What is the state of the thebesian vessels?

CAUSE AND MANNER OF DEATH

Many patients die soon after the artery is obstructed, in a second or in a few minutes. Is this a sudden stopping of the heart's action or is there a fibrillation of the ventricle that precedes death? When patients die suddenly as they often do, hours or days after the accident, is this due to suddenly developing fibrillation of the ventricle? Probably, yes, but it is not proved. How often is death due to rupture of the heart? How often to gradual heart failure with its ordinary symptoms—dyspnea, râles, cyanosis, edema, albuminuria? In how many cases is death due to a new thrombus that forms in some other artery of the heart? Is this, as Sternberg suggests, especially apt to occur in an artery at the edge of the infarct? Or is death often due to the increase of the original thrombus proximally, thus enlarging the area of infarcted and useless muscle?

INFLUENCE OF COMPENSATORY ENLARGEMENT OF ANASTOMOSING VESSELS

Paradoxical as it may sound, the heart whose vessels are extensively sclerosed may often better withstand the insult of sudden coronary occlusion than the one whose vessels are comparatively normal. If one of the coronaries is the seat of sclerosis that increases with advancing years, there may be a compensatory enlargement of the collateral and anastomosing branches. This feature with the description of the intricate capillary anastomosis is stressed by Oberhelman and LeCount in their article of 1924. The importance of the thebesian vessels in keeping alive a heart whose coronaries are extensively obstructed has been shown by Wearn, Scott and others.

It is only by recognizing the extensive intercommunication of blood vessels in the heart and the mutual dependence of one artery on the other that one can understand the ability of the heart to stand up under the shock of sudden occlusion of a large branch, a main trunk of a coronary, even the plugging of both coronaries, as in cases cited by Wearn and by Scott.

This question is worthy of still further study. Is there any way of deciding clinically by symptoms, by x-ray or electrocardiograph, what may be the prognosis? This depends largely, we may assume, on the condition of the intact portion of the heart muscle as well as on the capacity of the infarcted area to heal by scarring, and both these processes depend largely on the efficiency of the collateral circulation.

LOCALIZATION OF THE INFARCT

The immediate and remote effects of the accident will depend, not alone on the suddenness and completeness of the occlusion, but in large measure on the size and location of the artery involved, whether right or left coronary, descending or circumflex branch, small laterals, etc. Is it possible by symptoms, physical signs or instrumental aid to state the vessel occluded and the area of heart muscle secondarily damaged,

and thus gain knowledge that may be helpful in estimating the outcome or that may serve as a guide to treatment? Can we, in other words, localize the lesion as we do when a cerebral artery is occluded?

There is a difficulty in this problem that is inherent in the fact that the area of myocardial softening will depend much on the degree to which anastomoses are present and as already stated the degree to which compensatory changes have taken place in collateral vessels. In one heart the results of an occlusion near the origin of the descending branch of the left coronary artery may differ materially from a similar obstruction at the same place in another.

The electrocardiograph should here be extremely helpful. The fruitful experimental and clinical work of Fred Smith, Pardee, Parkinson and Bedford, and others is well known. But further animal investigation is desirable. Of greater value, however, will be the careful correlation of electrocardiographic study in man with check by postmortem findings. More accurate knowledge must surely come from such investigation.

It is probable, too, that we are not as painstaking in our examination of these patients as we should be. It would seem as though variations in the intensity and quality of pain and its radiation, in skin tenderness, dyspnea and cyanosis, drop in blood pressure, nausea, and vomiting, might all be significant, if properly analyzed, in helping to decide where the obstruction and the myocardial lesion lie. As is known, attempts have been made by Pletnew and by Libman, to differentiate between a lesion in the right coronary and in the left. In the former engorgement of the liver, in the latter dyspnea, fall in blood pressure, and other signs of pulmonary congestion are regarded as cardinal differentiating points. These observations should be continued. In this connection it must not be forgotten that the infarction effect of an obstruction of the left coronary is not limited to the muscle of the left ventricle nor does an obstruction in the right coronary soften only the muscle of the right ventricle. Not only are the septum and certain papillary muscles generally involved but there is more or less lapping over of the effect into the other ventricular wall in either case. This is because, as is well known, the right coronary artery sends a branch that goes to the posterior wall of the left ventricle. The left coronary helps supply a portion of the anterior wall of the right ventricle. So, pure right and pure left ventricular softening are not so very common.

X-ray examination may show the cardiac contour altered by the yielding, weakened wall. Possibly percussion may help in the same way. The location of a pericardial friction might at times be interpreted as indicating the location of the myocardial lesion. The problem of localization is therefore a live one and there are several avenues of approach.

PERICARDITIS

In what proportion of cases is the pericardium at autopsy found to be roughened? In how many of these has friction been heard? If not heard, does the location of the pericardial lesion posteriorly or laterally rather than anteriorly explain the failure to hear the abnormal sound, or is such failure due to lack of keen examination, or may such lesion exist and be noiseless? How often is there an infarct that, extensive in the subendocardial region, fails to reach the pericardium? Are the cases with friction more severe in type and of more serious prognosis than those without?

MILD TYPES

How often do mild types of the accident occur? All grades of severity exist. There are forms with instant death or death in a few minutes or hours; or with death postponed for days or even months. There is the form with stormy onset, severe reaction and then a recovery as regards life but with residual damage to the heart slight or serious as the case may be. There are mild cases, mild as to onset, as to early symptoms and late effects. That these mild cases are of greater frequency than is generally recognized is almost certain. Some of these patients fail to consult the doctor because the upset seems of no moment. Or the pain and other disturbances seem negligible to the physician and he fails to note slighter symptoms that are really full of meaning—slight drop in blood pressure, transitory dyspnea, moderate tachycardia, a trifling rise in temperature, or a little increase in the leucocytes. That these milder cases with prompt recovery are really of the nature of coronary thrombosis is at times shown by the fact that later a clear-cut attack of severer form may occur, recognized by patient and doctor as of the same character as the earlier mild one, differing chiefly in degree. Autopsy often reveals not only the recent infarct but also one or more older healed lesions with the anciently obstructed vessel.

In what way may these cases be recognized more definitely? By what grouping of historical data, symptoms, signs, and instrumental findings may we be able to state that this accident has occurred? Just as I have finished this paragraph there comes to hand the meaty article by Harold J. Stewart in the AMERICAN HEART JOURNAL for April, 1929. He expresses this same idea more succintly and forcefully than I have when he says: "The minimum signs and symptoms upon which one may venture to make a diagnosis of coronary occlusion and to give and estimate the state of the coronary vessels and of the heart muscle are not known."

The problem then is what are the minimum signs and symptoms?

RECURRENCES

How often are recurrences encountered? Surely not infrequently. It is almost a tradition that a patient who has had one cerebral stroke —a large proportion of such accidents being thrombotic—is liable to have another. Similarly a myocardial ictus, to use the French term, may be repeated. Recently at autopsy a fresh thrombus and infarct were found together with an old extensive scar with thinning of the walls, aneurysmal bulging, and obliterated coronary. The history recorded that seven years before, the patient had suffered a severe, painful, heart attack that had confined him to bed for many days.

Recurrences generally occur at shorter intervals than seven years. What is the rule as to time, if there is any rule? Are the recurrences as in the case cited due to new thrombi in other vessels, or are they oftener due to a proximal enlargement of the old thrombus?

PAINLESS ATTACKS

Among the outstanding symptoms in most descriptions of acute coronary occlusion is pain. This is generally described as sudden, often unprovoked by effort, severe, unyielding to nitroglycerin, requiring morphine. It may be typically anginal as to substernal location, brachial radiation, vise-like or gripping character. Often, however, it is low in the sternal region or is referred to the epigastrium.

But there is no doubt that there are cases with mild pain or with no pain at all. While in my own experience pain has been present in nearly all of the cases I have regarded as acute coronary occlusion, it has at times been absent or it has not been the earliest or most striking feature. In one case, otherwise perfectly typical, a weakness and dizziness marked the onset; and even several hours later there was no pain requiring morphine, merely a precordial distress. This substitution of sudden dyspnea for pain was aptly referred to by Obrastow and Strachesko as a pain equivalent. Rapid drop in blood pressure may be added to dyspnea as another pain equivalent. To what extent and in what way then may we recognize acute coronary occlusion in the absence of pain?

It may be added that when Gallavardin and other French writers say that pain is of secondary importance and a relatively rare incident in the clinical picture attending coronary occlusion, they are not drawing the line between acute or sudden obstruction of the artery that is attempted to be drawn here. If the ingravescent and slowly developing cases are included, pain undoubtedly is relatively much rarer.

Also, are pain and other typical features, as Wearn and others have noted, more apt to be lacking when an artery is obstructed in an individual whose heart is already failing, perhaps through old valvular

disease or degenerative myocardial processes? Is coronary obstruction extremely rare in association with auricular fibrillation, or is its apparent rarity due to the fact that it is easily overlooked because the well-known striking symptoms are missing? Are masked and atypical forms not unusual under these conditions?

ANGINAL PAIN BEFORE AND AFTER ATTACKS

There are quite divergent statements regarding the cessation or persistence of anginal pain after an acute coronary occlusion. In some instances no anginal manifestations have preceded the attack, and after the subsidence of the initial suffering no painful residue is left; there is no pain even on exertion. In other cases the occlusion ushers in a status anginosus generally resulting fatally in a few hours or in a few days. Or there may develop when the acuter symptoms have gone, the features of ordinary effort angina. On the contrary there are many instances where in a sufferer from angina, perhaps with hypertension, the painful paroxysms on walking have disappeared after the date of infarction. Some regard this as the almost invariable rule. There would seem to be, however, no justification for such a generalization; there seems to be no uniform result of the accident as regards pain of anginal character.

Further observations are desirable along this line. Perhaps some explanation may be offered for the various types of pain left after the occlusion.

BEARING ON THE THEORY OF ANGINA PECTORIS

What bearing has acute occlusion on the theories of angina pectoris? Without attempting to answer the question or to advance arguments it would seem that the phenomena attending the sudden obstruction of a coronary artery tend to strengthen the view that the paroxysm of angina of effort has its origin in a perversion of function of the coronary artery or the muscle supplied by such artery. The argument that claims the pain in this accident is an aortic pain seems far-fetched. Even if the painful stimulus is transmitted by way of the aorta, the origin seems to be in the coronary artery or in the heart muscle. This does not imply that there may not be pain of anginal character having its origin in a diseased aortic wall.

Closer study of cases of angina pectoris and of coronary thrombosis with animal experimentation may help solve this problem. There may arise occasionally in connection with accident or surgery the opportunity of studying in man, in vivo and without an anesthetic, the effect of obstructing the coronary artery. Some cardiac Beaumont may find his Alexis St. Martin.

DEATH IN ANGINA PECTORIS DUE TO ACUTE CORONARY OCCLUSION

Sudden death is common in angina pectoris. How often is this due to the acute obstruction of a coronary artery? Probably the percentage of such deaths attributable to coronary obstruction will decidedly increase if careful autopsy investigation is made. LeCount's figures on coroner's cases are highly suggestive.

CRITERIA OF DIAGNOSIS

Generally easy to recognize if once thought of, this condition may be most perplexing. Are there helps to diagnosis that may be added to those already available? Critical and prompt decisions as to operation for suspected surgical accidents have to be made at times. Detailed reports of such cases will be helpful.

ATYPICAL CASES

Reference has already been made to certain variations from the type, especially as regards pain. Others might be mentioned. Dyspnea, often striking, merging into Cheyne-Stokes breathing may be present. Yet it may not be noticed. Blood pressure commonly drops, a most valuable symptom. Yet at times it holds up remarkably well, and unexplained daily or hourly striking variations in pressure are sometimes noted. The rate and rhythm of the pulse may be freakish. There may be little change from normal. The electrocardiogram may also be freakish. Dr. Walter Hamburger showed me the tracings in a hospital patient where extrasystoles from different foci, partial and complete block, paroxysms of tachycardia and of fibrillation had alternated with one another in an almost unbelievable manner during the several weeks following the seizure. Temperature is not always elevated. Subnormal temperatures have been reported. And there are other variations. This may increase the difficulties of diagnosis, but the study and reporting of these atypical cases will help establish rules for diagnosis.

TREATMENT

That rest and morphine do good or may save a life is generally believed. But how long in bed? What drugs? Is digitalis helpful or harmful? Does nitroglycerin do any good? Or do the theobromine compounds? Can anything be done to ward off an attack or a recurrence, e.g., by treating infections in one suffering from angina pectoris or from hypertension? Further careful observations like those of Levine on the helpful effects of quinidine, or of Allan on the use of glucose, are needed.

In conclusion to repeat what was said at the beginning, this paper is but an outline. It is intended to be suggestive. It is hoped it may stimulate to a further study of this interesting and important condition that is not yet by any means thoroughly understood.

FURTHER EXPERIENCES WITH VENESECTION IN CONGESTIVE HEART FAILURE*†

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IN 1927 Eyster and Middleton[1] reported the results from venesection in a series of 21 cases of congestive heart failure. Their experience reaffirmed the value of this procedure in relieving right heart strain. Venous pressure determinations served as a guide to venesection in this clinical study, 20 cm. of water constituting the critical level, after the work of Clark.[2] It was furthermore established that the trend of the venous pressure curve subsequent to venesection served as an excellent measure of its efficacy. Almost invariably the venous pressure of the decompensated individual fell sharply on blood-letting. In the favorably reacting cases whose myocardial reserve was sufficient to meet the decreased diastolic load by a more adequate contraction, the venous pressure remained low and even tended to approach the normal level after the primary fall. On the other hand in the cases possessing an insufficient myocardial reserve, the temporary respite of a lessened diastolic filling was not adequate to initiate such a cycle. Hence the advantage of a lowered venous pressure from venesection was not maintained, and it thereafter mounted steadily to or above its previous level. Obviously such a distinction in the venous pressure curves following blood-letting in congestive heart failure must lend a considerable prognostic importance to such studies.

In the eighteen months elapsing since that report an additional group of 22 cases of congestive heart failure has been subjected to venesection. In addition to the usual subjective and objective criteria of right heart overload the determination of venous hypertension by the indirect method of Hooker and Eyster[3] again served as the final judgment. A venous pressure of 20 cm. of water, either maintained or ascending, was deemed adequate grounds for venesection. In Table I are listed the clinical data on the cases of this group.

An analysis of this table revealed a preponderance of cases with a myocardial degenerative background. Arteriosclerosis was the predominant etiological factor. The age grouping (9 in the fifth decade, 4 in the sixth and 9 over 60 years of age) undoubtedly determined this factor in a measure. Of the 22 cases only 3 were females. As to the remote and the recent occurrence of decompensation no relation was borne in the results from venesection.

A total of 26 venesections was performed on the 22 subjects; and in

*From the Department of Medicine, University of Wisconsin.
†Read before the Wisconsin Heart Club, April 19, 1929.

TABLE I.

NO.	AGE	SEX	BASIC LESION	ETIOLOGY	OCCURRENCE-DECOMPENSATION		V.P. CM. H_2O	AMOUNT BLOOD LET (CC.)	RESULTANT V.P.			EFFECT	
					REMOTE	PRESENT			LOWEST (CM. H_2O)	INTERVAL	DURATION	IMMEDIATE	ULTIMATE
1	47	M	Endocarditis	Rheumatic fever	3 years	3 mos.	18	550	8	Immediate	24 hrs. later 12 cm.	Improvement marked and immediate	13 days later V.P. 20 and return of cyanosis for short time; 17 days after venesection V.P. 7 and steady improvement in circulatory status
2	42	F	Endocarditis	Rheumatic fever	5 years	3 mos.	20	600	12	Immediate	24 hrs. later 16 cm. but fell to 12 on 4th day	Cyanosis cleared and there were fewer basal rales. General condition less affected	Steady improvement in general circulatory condition
3	72	M	Myocardial degeneration	Nephritis with hypertension	——	8 mos.	23	500	10	Immediate	Maintained for 2 days, then rose to 19 cm.	Early improvement objectively and subjectively	Hydrothorax reaccumulating led to repeated aspirations Death 42 days later
4	46	M	Myocardial degeneration; fibrinous pericarditis	Broncho-pneumonia; empyema	——	3 days	30	600	24	½ hour	9 hrs. later 20 cm.	Rallied slightly but anoxemia supervened	Oxygen controlled condition for time. Death 31 hours
5	53	M	Myocardial degeneration	Arteriosclerosis	——	4 mos.	24	500	14	½ hour	2 hrs. later 17 cm.	Cyanosis and dyspnea much improved	Improvement maintained for ten days
						Eleven days later	20	550	14	12 hours	?	Marked subjective improvement	Died 39 days after second venesection, apparently from effort of defecation. V.P. ran from 12 to 14 cm. in interval
6	74	M	Myocardial degeneration	Arteriosclerosis; hypertension	——	3 mos.	? edema	500	? edema	? edema	V.P. 14, 24 hrs. later	Pronounced relief in respiratory difficulty and pulmonary edema	Maintained improvement. Discharged 44 days later. V.P. ranged 8 to 14 cm. in interval
7	76	M	Myocardial degeneration	Arteriosclerosis; hypertension	2 years	3 mos.	26	500	10	Immediate	V.P. 16, 48 hrs. later	Remarkable improvement	V.P. ranged from 7 to 14 cm. until discharge 148 days later
8	50	F	Endocarditis; Myocardial degeneration	Rheumatic fever; hypertension	2 years	4 mos.	28	550	12	1 hour 20 min.	Maintained	Marked subjective improvement	V.P. 6 to 14 cm. until discharge 96 days later; convalescence not smooth, however.
9	41	M	Myocardial degeneration	Arteriosclerosis; bronchial asthma	——	7 mos.	18	500	8	½ hour	V.P. 12 cm. 24 hrs. later	Marked immediate relief	V.P. 10-15 cm. for 26 days and improvement maintained. On 27th day rise of V.P. with return of dyspnea and cyanosis
						Twenty-seven days later	18	600	9	35 min.	V.P. 14 cm. 4 days later	Much easier breathing and greater comfort	Steady higher level maintained after 4th day with general vascular slump, V.P. running from 12 to 23 cm. before death on 33rd day after 2nd venesection

TABLE I—CONTINUED

NO.	AGE	SEX	BASIC LESION	ETIOLOGY	OCCURRENCE-DECOMPENSATION		V.P. CM. H_2O	AMOUNT BLOOD LET (CC.)	RESULTANT V.P.			EFFECT	
					REMOTE	PRESENT			LOWEST (CM. H_2O)	INTERVAL	DURATION	IMMEDIATE	ULTIMATE
10	69	M	Myocardial degeneration	Arteriosclerosis; hypertension	——	3 mos.	20	550	9	5 min.	24 hrs. later V.P. 12 cm.	Decided improvement in all details except psychic state	Objective and subjective improvement progressive and satisfactory until discharge 22 days later, highest V.P. 13 cm.
					Readmitted 122 days later								
							23	550	16	1 hour	Maintained	Much improved, Fell to sleep after procedure	Cyanosis and dyspnea relieved but V.P. only slowly fell to 7 cm. 11 days later
11	47	M	Endocarditis	Rheumatic fever	3 years	4 mos.	18	550	11	1 hour	Maintained for 2 days	Improvement objectively, Cheyne-Stokes respiration relieved	Two days later able to lie flat on back. V.P. 5-15 cm. until discharged 17 days later
12	46	F	Endocarditis	?	——	10 mos.	22	500	?	?	?	Slight improvement	Died in 24 hours
13	64	M	Myocardial degeneration	Arteriosclerosis; hypertension	——	2 weeks ?	20	510	14	2½ hours	Maintained	Relief of pressure sense in abdomen; cyanosis and dyspnea little affected	Died five days later
14	43	M	Myocardial degeneration	Hypertension	2 years	2 mos	23	500	14	Immediate	Fell to 8 cm. in 48 hrs.	Relief of dyspnea	Periodic dyspnea and pulmonary edema recurred. V.P. usually between 10 and 12 cm.
					Forty-one days later								
							? edema	475	? edema	——	——	No relief	Died 115 days later
15	64	M	Myocardial degeneration	Arteriosclerosis	4 years	3 mos.	?	520	10	Immediate	V.P. 21 cm. 2 days later	Early improvement in respiration, subjectively much better	Improvement not sustained, but after a period of 5 days slumped and died
16	63	M	Myocardial degeneration	Arteriosclerosis; hypertension	?	?	23	400	20	Immediate	——	No improvement	Died 6 hours later
17	62	M	Myocardial degeneration	Arteriosclerosis; hypertension	4 years	9 mos.	24	500	15	1 hour	24 hrs. later V.P. 14 cm.	Little change in general condition	Water balance remained poor, and subject died 10 days later of cerebral accident
18	43	M	Myocardial degeneration	Silicosis	4 years	4 mos.	24	500	8 ?	15 min.	Not maintained	No relief of pulmonary edema.	Died 4 hours later. Cyanosis and dyspnea unchanged by procedure and V.P. rapidly mounted
19	47	M	Endocarditis	Rheumatic fever	3 years	3 mos.	20	500	12	Immediate	12 cm. for 12 hrs; 14 next day	Marked improvement. Relief of cyanosis and dyspnea	Advantage held for 48 hours. Then V.P. rose to 18 but fell gradually and progress was satisfactory
20	50	M	Myocardial degeneration	Syphilis	1 year	6 mos.	? edema	500	? edema	——	——	Slight improvement in cardiac action	Death in 3 hours
21	62	M	Myocardial degeneration	Arteriosclerosis; hypertension	——	4 days ?	20	550	14	2 hours	6 hrs. later 16 cm.	Definite improvement in all details	In 48 hours further fall of V.P. to 10 cm. and continued progress; 2 thoracenteses apparently important in determining change
22	57	M	Myocardial degeneration	Arteriosclerosis	7 mos.	3 days	28	550	13	2½ hours	Maintained	Marked improvement	Marked diuresis on second day; V.P. remained low.

accord with the precept of Meek and Eyster[1] 500 c.c. of blood was, as a rule, withdrawn. On two occasions a somewhat smaller quantity was taken, but in 12 instances a larger amount was let. The immediate results were favorable in 11 of the 18 individuals who were bled a single time, and on 7 of the 8 occasions where a second phlebotomy was required in the remaining 4 subjects. Hence, it may be stated that the early response to venesection was satisfactory in 14 of 22 cases of congestive heart failure. An interesting correlation was established between the degree of venous pressure fall and the immediate clinical response to the procedure. Arbitrarily a fall of 8 cm. of water venous pressure was considered an adequate immediate response to venesection (500 c.c. of blood). On this basis 13 cases reacted favorably; and of these, a total of 11 showed definite clinical improvement. The corollary unfortunately does not hold; failure to effect an adequate fall in the venous pressure does not necessarily exclude a clinical advantage from the procedure, as witness cases 5 and 10 (second blood-letting) and 11 and 21 (single venesection).

The ultimate outcome of this group of 22 cases was quite illuminating. Only 10 individuals left the hospital. On the other hand, of the 12 cases terminating fatally, 5 survived the venesection by longer than a week, a limit which was arbitrarily set by Eyster and Middleton[1] as a fair indication of survival from the emergency which had led to venesection. The days of death after venesection in these cases were 42, 39, 33, 115, and 10, respectively. Two other cases survived 5 days and the remaining 5 fatal cases, 31, 24, 6, 4 and 3 hours, respectively. Clearly the last-mentioned group of 5 fatal cases (Nos. 4, 12, 16, 18 and 20) constitute a type in which hindsight might well condemn the plan of attack. It is interesting, too, that not a single case of this limited group showed early amelioration of right heart distress, and only 1 (Case 18) possibly fell in the group in which an adequate venous pressure fall was noted.

Characteristic clinical responses to venesection are abstracted in the following contrasting reports:

CASE 4.—A white male, 46 years old, was admitted to the Wisconsin General Hospital, Feb. 6, 1929, with a history of a cough of 6 weeks' duration. Examination resulted in a diagnosis of bronchopneumonia with empyema (left). Three days later an accession of dyspnea and cyanosis was accompanied by a venous pressure of 30 cm. of water. A venesection was performed and 600 c.c. of blood let. Immediately thereafter the venous pressure reading was 27 cm. and in one-half hour the low level of 24 cm. was established. A subsequent rise to 26 cm. was recorded in another half hour. Although the evidences of anoxemia were partially controlled by oxygen, the circulatory balance was never restored, and the patient died in 31 hours after venesection. In addition to the anticipated pleuropulmonary changes, necropsy revealed a serofibrinous pericarditis, cardiac hypertrophy and dilatation and fibrous myocarditis.

CASE 19.—A white male, 47 years old, was admitted to the Wisconsin General Hospital, March 23, 1929, complaining of dyspnea and weakness. A background

of rheumatic fever was established for the picture of cardiac decompensation, which included in addition to the subjective complaints above mentioned, generalized edema, nausea, vomiting, cough, cyanosis, congestive râles, cardiac enlargement, auricular fibrillation, hepatic engorgement, positive centrifugal venous pulse and ascites. A day's rest and medication failing to stabilize the circulatory condition and a venous pressure of 18-20 cm. of water pertaining, 500 c.c. of blood was withdrawn. During the course of the phlebotomy the patient expressed marked relief in the respiratory oppression, dyspnea subsided, and the cyanosis was lessened. Immediately after the venesection, the venous pressure registered 12 cm. of water and so remained for 12 hours. With but one temporary slump the advantage gained from venesection was maintained.

A comparison of results between the previously reported cases[1] and the present group would seem justified by the parallelisms in numbers, types, technic and controls. Eyster and Middleton[1] reported immediate improvement in 15 of 21 cases (71.4 per cent) as compared with 14 and 22 (63.6 per cent) in the present series. The ultimate results on the other hand indicate a more favorable response in the present group, 10 of 22 cases (45.4 per cent) surviving as compared with 6 of 21 (28.5 per cent). As in the earlier experience, a favorable primary response to venesection constituted a good prognostic sign, in that even the fatally terminating cases enjoyed a disproportionately extended length of life as compared with those showing no such immediate improvement after venesection. This rule held in all except Case 14 after the second venesection.

SUMMARY

In conclusion it may be granted that the immediate results from venesection of 500 c.c. in congestive heart failure are frequently spectacular and in a majority of instances, beneficial. From the very nature of the cases selected for this procedure ultimate recovery is not anticipated in a high proportion. Nevertheless, a survival of 45.4 per cent is reported in this group and an apparent prolongation of life claimed in an added 22.7 per cent (5 cases). The application of such a mechanical therapeutic measure as venesection offers a field of particular usefulness for venous pressure determinations, in that not only does venous hypertension constitute an index of right heart load, but the degree of primary fall in venous pressure on blood-letting and the curve thereafter serve as excellent prognostic measurements of its efficiency.

REFERENCES

1. Eyster, J. A. E., and Middleton, W. S.: Venous Pressure as a Guide to Venesection in Congestive Heart Failure, Am. J. M. Sc. **174**: 486, 1927.
2. Clark, A. H.: A Study of the Diagnostic and Prognostic Significance of Venous Pressure Observations in Cardiac Disease, Arch. Int. Med. **16**: 587, 1915.
3. Hooker, D. R., and Eyster, J. A. E.: An Instrument for the Determination of Venous Pressure in Man, Bull. Johns Hopkins Hosp. **19**: 274, 1909.
4. Meek, W. J., and Eyster, J. A. E.: Reactions to Hemorrhage, Am. J. Physiol. **56**. 1, 1921.

THE USE OF CALCIUM CHLORIDE GIVEN INTRAVENOUSLY IN CONGESTIVE HEART FAILURE*

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IT HAS long been known that the presence of calcium ions is necessary to the function of contraction of heart muscle. Merunowicz[1] in 1875 first observed that the aqueous extract of ash when used as a perfusate would support contraction of the heart. It remained for Ringer,[2] however, to discover the necessity of the presence of calcium ions in the perfusion fluid. Following these observations, the study of ions in relation to the heartbeat was extended by Howell,[3] Loeb,[4] Burridge,[5] Mines[6] and others until it was finally established that the presence of calcium ions is necessary for the mechanism of contraction of heart muscle, while the presence of potassium ions is necessary for that of relaxation, and that the principal function of sodium ions is to maintain the proper relations of osmotic pressure. In the study of the pharmacological action of digitalis an attempt has been made to connect the action of digitalis with the presence of sodium, potassium or calcium ions. Clark[7] in 1912 published experiments on the perfused hearts of frogs which led him to conclude that the systolic action of digitoxin upon the frog's heart was dependent upon the presence of calcium ions, that diminution of the quantity of calcium in Ringer's solution diminished the systolic action of digitoxin while the presence of an excess of these ions did not influence the systolic action of digitoxin. Konschegg,[8] however, from data also obtained from perfusion experiments, came to an opposite conclusion, namely, that a strophanthin (digitalis) effect was not connected with the presence of calcium since the drug was still effective in hearts which had been washed free of this ion by prolonged profusion.

In 1917 Loewi[9] made a report of perfusion experiments bearing on this subject. He concluded that a strophanthin (or digitalis) effect consists only in making the heart muscle receptive to calcium ions; increased receptiveness is followed by an increased calcium effect. It is the function of digitalis bodies, in other words, merely to sensitize the heart muscle to the action of calcium which is already present in the circulating blood. He was of the opinion that the proportion of calcium was not lowered in cases of heart failure but that the sensitiveness of the heart muscle to the concentration of calcium present in the blood was diminished. Digitalis acts by restoring the sensitiveness of heart muscle to that concentration of calcium. The same result was

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said to be attainable if the level of calcium in the blood was temporarily raised by injecting calcium intravenously. Singer[10] on the basis of Loewi's experiments began injecting calcium chloride intravenously in the treatment of congestive heart failure. He reported excellent diuretic effects from its use. Later, he administered digitalis orally or intravenously simultaneously with the injection of calcium chloride intravenously. His results were striking in that diuresis amounting to from 7000 c.c. to 8000 c.c. per day was reported. Hellmann and Kollmann[11] confirmed these results in case of "Aortenfehlern" and "Myodegeneratio cordis." Loewenberg[12] observed similar effects following the intravenous injection of calcium chloride.

We are now reporting our experience with the intravenous injection of calcium chloride.

We have approached the problem from two points of view. In the first place we wished to ascertain whether calcium chloride in the amounts administered had an effect on the function of contraction of heart muscle in man, and in the second place we wished to test its diuretic effect in cases of congestive heart failure.

Before giving calcium chloride intravenously to patients we took the precaution of making preliminary observations on dogs with a view to learning the dose with which toxic effects on the heart were induced.

We injected calcium chloride (10 per cent solution), 0.5 gm. to 1.1 gm., intravenously in dogs without the appearance in the electrocardiograms of ventricular premature contractions or ventricular standstill. In one dog we injected intravenously at the same time calcium chloride, 0.5 gm. and 30 per cent of the calculated lethal dose of tincture of digitalis (Upsher Smith). About forty minutes after the injection frequent ventricular premature contractions occurred and were still present one and one-half hours after the injection; they were no longer present the next day. One week later the experiment was repeated and similar results were obtained. One week later still, a smaller dose (25 per cent of the calculated lethal dose) of the same tincture was injected with the same amount of calcium chloride. In this case irregularity did not occur. A second dog was given 25 per cent of the calculated lethal dose of the tincture of digitalis intravenously without causing an irregularity. Two hours later calcium chloride, 0.5 gm., was given intravenously and ventricular premature contractions failed to develop. One week later, when 30 per cent of the calculated lethal dose was injected followed by the same amount of calcium chloride, a slight extrasystolic irregularity developed. It appears then that 30 per cent of the calculated lethal dose of digitalis is critical when combined with the injection of calcium chloride.

To study the effect of calcium ions on the functions of contraction we used the method of the moving x-ray films which was adopted by Cohn and Stewart[13] in their study of the effect of digitalis on contrac-

tion in the human heart muscle. This method consists in photographing with roentgen rays the excursions of the two borders of the heart. By this method continuous curves are obtained, the curves recorded representing the shortening or contraction undergone during systole by that portion of the left ventricular and right auricular margins which are photographed. The apparatus and technic of obtaining these curves has been described by Cohn and Stewart. These observations were made in male patients, the subjects of heart disease whose chests were reasonably thin and who were free of edema.

Preliminary moving x-ray photographs were taken at the level of the apex of the heart. This level was marked on the patient's chest. Immediately afterward the patient lay down and sterile calcium chloride (10 per cent solution) was injected intravenously. Moving x-ray photographs were then made at the same level as that at which the preliminary curve had been taken, the exposures being made at intervals ranging from two to thirty minutes after the injection. A series of such photographs was made of patients who had not received digitalis. In a second series of patients digitalis was given until by electrocardiograms (T-wave and conduction changes) and clinically (in auricular fibrillation slowing of ventricular rate) a digitalis effect was observed. After preliminary moving x-ray photographs were made of these patients, calcium chloride was given intravenously, and x-ray moving films were again taken, exposed as in the first instance. Both series of observations were made in patients in whom the rhythm was normal as well as in those who exhibited auricular fibrillation. Only those curves were measured in which the stationary films taken at the time the moving films were exposed showed that identical points on the left ventricular margin had been exposed in the photographs taken after injecting calcium chloride as had been exposed in the preliminary films. The excursions made by the heart's border were traced on tissue paper and the height of the left ventricular excursions measured in the manner described by Cohn and Stewart.[13]

The method of injecting calcium chloride was as follows. A venepuncture needle to which a Luer syringe was attached was inserted into a cubital vein. A small amount of blood was withdrawn in order to be certain that the needle had entered the vein. With the needle left in place this syringe was disconnected and one containing calcium chloride solution was substituted for it. Calcium chloride was injected slowly. The technic described avoids the danger of introducing calcium chloride into the subcutaneous tissues. If this occurs, necrosis of the tissues is said to take place. During injection the patients described a sensation of heat in the blood vessels as the calcium chloride was carried through the body. A few patients called attention to a salty taste. No untoward effects were observed either during or following injection. We have made studies of six patients; in four,

observations were made before they received digitalis and again after digitalis had been given. Of one patient, only, those photographs taken during the calcium chloride period were suitable for measurement, while of the sixth patient, the curves were measurable only in those photographs taken when calcium chloride was given at the time the patient was under the influence of digitalis.

A complete protocol is given in one case only.

CASE 1.—R. McCl. was a male, 18 years old. He complained of shortness of breath, weakness, loss of appetite and precordial pain of several months' duration. He had suffered from chorea in childhood. The tonsils were excised first when he was 6 years old. Frequent attacks of tonsillitis occurred from 1915 to 1920. There was an attack of acute rheumatic fever in 1916. In 1924 the tonsils were removed again. Since the last tonsillectomy there had been no attacks of acute tonsillitis. He was well from 1924 until the onset of the present illness.

Physical Examination.—The patient was a well-nourished, well-developed youth. He lay flat in bed without respiratory distress. There was no cyanosis. The teeth were in excellent condition. The tonsils had been cleanly removed. The heart was slightly enlarged. There were no thrills over the precordium; the heart sounds were essentially clear both at the apex and over the base, except for a presystolic element in the abrupt first sound. The second pulmonic sound was reduplicated. The heart rate was slow. The rhythm was regular except for occasional premature contractions which were followed by short compensatory pauses. The systolic blood pressure measured 100 mm. of mercury and the diastolic 70 mm. The lungs were clear. The abdomen was negative. There was no edema. The Wassermann reaction in the blood was negative. The urine was negative. The phenolsulphonephthalein excretion, the concentration and dilution tests for water excretion, and the index of urea excretion, all showed normal values. The leukocyte count varied between 11,000 and 15,000 when he was first admitted to hospital but later fell to 8,000. The count of the red blood cells was 7,000,000. The oxygen capacity of the blood was 10.28 mM. O_2, which is equivalent to 124 per cent hemoglobin. The electrocardiogram showed a normal rhythm and the conduction time was normal. There were occasional premature contractions.

On March 7, the patient was under the influence of digitalis; the left ventricular excursion at the level of the fourth interspace measured 5.2 mm. (Table I). Ten minutes after the intravenous injection of calcium chloride 0.5 gm. the excursion was 5.5 mm., that is to say it was substantially unchanged.

On March 9 the patient was still under the influence of digitalis; the left ventricular excursion measured 5.7 mm. Eleven minutes after calcium chloride, 0.6 gm., had been injected, it was 5.5 mm.; 22 minutes afterward it was 5.9 mm., that is to say the extent of ventricular contraction was unchanged. It may be recalled that 1 mm. is within the limits of error of measuring these curves. The patient received no digitalis for 10 days. On March 17 the excursion at the level of the fourth interspace was 5.4 mm. Ten minutes after the injection of calcium chloride, 0.8 gm., it was 6 mm., and 28 minutes afterward 6.4 mm. On April 10 when the patient was not under the influence of digitalis, the left ventricular excursion was 6.1 mm. The excursion was 5.9 mm. 6 minutes after the injection of calcium chloride, 0.8 gm., and 24 minutes afterward 7 mm. He was then given digitalis. On April 14 the left ventricular excursion was 7.2 mm.; 10 minutes after the injection of calcium chloride, 0.8 gm., it was 7.2 mm.; 20 minutes afterward it was 6.5 mm. It is clear then that calcium chloride did not increase the extent of contraction of the left ventricle either when it was given alone or when the patient was under the influence of digitalis.

TABLE I

EFFECT OF THE INTRAVENOUS INJECTION OF CALCIUM CHLORIDE UPON THE VENTRICULAR EXCURSION IN CASE 1. NORMAL RHYTHM

DATE	FILM NO.	INTERCOSTAL SPACE PHOTOGRAPHED	TRANSVERSE DIAMETER OF CONTROL FILM AT LEVEL PHOTOGRAPHED	ANALYSIS OF MOVING FILM					ANALYSIS OF STATIONARY FILM									
				TRANSVERSE DIAMETER OF TRACING IN INSPIRATION		LEFT VENTRICULAR EXCURSION	RIGHT AURICULAR EXCURSION	HEART RATE	CARDIAC AREA	MIDDLE LINE TO LEFT BORDER	MIDDLE LINE TO RIGHT BORDER	TRANSVERSE DIAMETER	LONG DIAMETER	ANATOMICAL ANGLE	DIGITALIS	CALCIUM CHLORIDE INTRAVENOUSLY	TIME WITH REFERENCE TO INJECTION OF CALCIUM CHLORIDE
				SYSTOLE	DIASTOLE												
			cm.	cm.	cm.	mm.	mm.	per minute	sq. cm.	cm.	cm.	cm.	cm.	degrees	gm.	gm.	
March 7, 1925	i	4	11.5	11.8	12.6	5.2	3.1	120	*94.0	7.6	4.0	11.6	13.2	41.0	+	0.5	Before
	ii	4	11.7	11.9	12.8	5.5	3.2	115	91.9	7.6	4.1	11.7	12.9	40.0			10 minutes after
March 9, 1925	i	4	12.0	12.5	13.4	5.7	3.9	96	97.5	8.4	3.9	12.3	13.9	35.0	+	0.6	Before
	ii	4	12.0	11.9	13.2	5.6	5.3	96	101.6	7.9	4.3	12.2	13.7	39.0			11 minutes after
	iii	4	12.5	12.5	13.5	5.9	4.0	96	109.7	8.0	4.6	12.6	14.1	40.0			22 minutes after
March 17, 1925	i	4	12.5	12.6	13.3	5.4	2.6	120	108.5	8.5	4.5	13.0	14.4	37.0	0 (none since 3/7/25)	0.8	Before
	ii	4	12.3	12.0	13.0	6.0	3.5	108	103.4	8.0	4.6	12.6	14.0	36.0			10 minutes after
	iii	4	12.0	12.5	13.5	6.4	2.9	108	93.0	8.0	4.1	12.1	13.9	38.5			28 minutes after
April 10, 1925	i	4	11.7			6.1		Time marker indistinct	94.2	8.2	3.7	11.9	13.9	34.0	0	0.8	Before
	ii	4	11.9			5.9			97.9	7.9	4.1	12.0	13.8	36.0			6 minutes after
	iii	4	12.5			7.0			103.0	8.3	4.3	12.6	14.2	37.0			24 minutes after
April 14, 1925	i	4	12.4	12.5	13.6	7.2	3.0	110	98.0	8.3	4.0	12.3	13.8	39.0	+	0.8	Before
	ii	4	12.7	13.0	14.4	7.2		96	100.3	8.3	4.3	12.6	13.6	35.0			10 minutes after
	iii	4	12.7	13.4	14.2	6.5	2.5	108	100.7	8.2	4.6	12.8	14.1	37.0			20 minutes after

TABLE II

SUMMARY OF THE OBSERVATIONS ON THE EFFECT OF CALCIUM CHLORIDE ON THE LEFT VENTRICULAR EXCURSION OF THE HEART

	RHYTHM	CASE NO.	NUMBER OF OBSERVATIONS	EFFECT ON LEFT VENTRICULAR EXCURSION	DIAGNOSIS*
Calcium chloride	Normal	Case 1	2	0	A: Acute rheumatic fever (inactive). B: Chronic myocarditis. C: Normal sinus rhythm; auricular premature contractions; cardiac pain.
		Case 2	1	0	A: Acute rheumatic fever (?). B: Cardiac hypertrophy; mitral stenosis and insufficiency; right ventricular preponderance. C: Normal sinus rhythm.
		Case 3	3	0	A: Acute rheumatic fever (inactive); chronic nephritis. B: Mitral insufficiency; cardiac hypertrophy; right ventricular preponderance. C: Normal sinus rhythm; arterial hypertension.
		Case 4 (Outpatient)	1	0	A: None. B: None. C: Normal sinus rhythm; cardiac pain.
	Auricular fibrillation	Case 5	4	0	A: Acute rheumatic fever (?). B: Mitral stenosis and insufficiency; aortic insufficiency; cardiac hypertrophy. C: Auricular fibrillation.
Calcium chloride and digitalis	Normal	Case 1	3	0	
		Case 2	1	0	
		Case 3	1	0	
	Auricular fibrillation	Case 5	5	0	
		Case 6	1	0	A: Acute rheumatic fever (?). B: Mitral stenosis and insufficiency; cardiac hypertrophy. C: Auricular fibrillation.
Total: Calcium chloride			11	0	
Calcium chloride and digitalis			11	0	

*The diagnoses conform to the nomenclature for cardiac diagnosis approved by the American Heart Association. AM. HEART J. 2: 202, 1926.
A = Etiological.
B = Anatomical.
C = Physiological.

Since the observations on all six patients yielded similar results they are not reported in detail. The data of all the patients are, however, summarized in Table II. Calcium chloride was given on seven occasions to four patients in whom the cardiac rhythm was normal and on four occasions to one patient the subject of auricular fibrillation. The extent of contraction of the left ventricle was not influenced by the drug in a single instance. It was given on five occasions

to three of the patients exhibiting a normal rhythm who had beforehand been given digitalis, and on six occasions to two patients, subjects of auricular fibrillation while under the influence of digitalis. In these instances also the injection of calcium chloride failed to induce a change in the extent of the left ventricular excursions. Since Cohn and Stewart[13] have shown that therapeutic doses of digitalis give rise to increases in the contractions of the left ventricle, we conclude that calcium chloride in the doses given does not affect the extent of contractions of the left ventricle, at least at the point of the ventricular margin which we studied.

There is, however, the possibility that calcium chloride might influence the force of ventricular contraction, although it does not affect the extent of contraction. Patients in whom the auricles are fibrillating lend themselves to the study of this phase of the problem. If

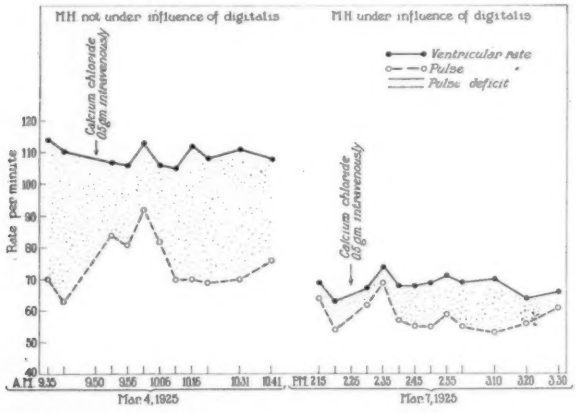

Fig. 1.—This shows the effect of intravenous injection of calcium chloride on the ventricular and on the radial pulse rate in Case 6.

the force of ventricular contractions increased following the injection of calcium chloride, a greater number of cardiac systoles may be forcible enough to open the aortic valves and to force blood into the vascular system; the pulse deficit will then be diminished. The patients studied from this point of view were at rest for one-half hour or longer. The ventricular rate at the apex and the pulse rate in one radial artery were counted simultaneously several times at intervals of a few minutes and the pulse deficit recorded. Calcium chloride was then given intravenously; the pulse rates were counted again at intervals of a few minutes until the end of one hour. These observations were made in several patients before digitalis was given and later also when the patients were under the influence of this drug. The injection of calcium chloride did not decrease the pulse deficit appreciably (Fig. 1); although it appeared that when the patient was not under the influence of digitalis and calcium chloride was injected, it was slightly

less for a few minutes after its injection, that is to say the number of effective beats was slightly larger; this effect, however, was only transitory. The results in the other patients were identical. No evidence is gained then from these observations that calcium chloride influences more than transiently the force of the ventricular contraction either if given alone or if given when the patient is under the influence of digitalis.

To ascertain the effect of calcium chloride upon the heart muscle three patients, subjects of auricular fibrillation, and three patients in whom the cardiac rhythm was normal were studied electrocardiographically. In two patients of each group observations were made when they were under the influence of digitalis as well as when they were not. They were given a preliminary period of rest varying from thirty to sixty minutes. Electrocardiograms were taken immediately before and at intervals of a few minutes after the injection of calcium chloride until the end of one hour. No changes were observed either in the form of the electrocardiogram, in conduction time in cases of normal rhythm or in the ventricular rate following the injection of calcium chloride.

There is then no evidence that calcium chloride in the doses given influences either the force or the extent of contraction of the heart, or that the heart muscle is affected by it, at least in respect to the observations which were made.

The use of calcium chloride administered intravenously as a diuretic.—Following Singer's[10] recommendation calcium chloride was given intravenously to twelve patients with edema of cardiac origin. All patients remained in bed until the effects of rest and of restriction of the intake of fluids had been established. Calcium chloride was then given intravenously both to those who were not and to others who were under the influence of digitalis; in a third set of observations digitalis was administered after the injection of calcium chloride. The report of these observations follows.

CASE 8.—G. E. This patient was a male, 58 years old. The cardiac diagnosis was as follows: *Etiological:* arterial hypertension; *anatomical:* cardiac hypertrophy, chronic myocarditis, slight right ventricular preponderance; *physiological:* normal sinus rhythm, congestive heart failure. The signs of congestive heart failure were hydrothorax and edema. The Wassermann reaction of the blood was negative. The systolic blood pressure measured 160 mm. of mercury and the diastolic 120 mm. The patient suffered a first attack of congestive heart failure one and one-half years ago. The present one was the third. Tremendous diuresis occurred when the patient was resting in bed and the fluid intake limited. It continued for many days. He became free of edema. When he began sitting up edema recurred. The patient was allowed to sit up the same number of hours each day. He was given calcium chloride, 0.1 gm., intravenously each night. On the fourth day there was a slight increase in the volume of urine. It was injected on four subsequent nights. The variation was no greater, however, than it had frequently been before the injection of calcium chloride. He was finally made free of edema by taking

digitan 0.5 gm. every 2 weeks and this state has been maintained even after he returned to work. It was in patients like this one that Singer thought the intravenous injection of calcium chloride particularly effective. Diuresis did not occur, however, in this instance.

CASE 9.—M. K. This patient was a male, 12 years old. The cardiac diagnosis was: *Etiological:* acute rheumatic fever (inactive); *anatomical:* mitral stenosis and insufficiency, tricuspid insufficiency, cardiac hypertrophy, right ventricular preponderance; *physiological:* normal sinus rhythm, congestive heart failure. The signs of congestive heart failure were edema, right hydrothorax, ascites and enlargement of the liver. This was the first attack of congestive failure. It was of one month's duration. Digitalis and theobromine diuretics were without diuretic effect. When the patient was not under the influence of digitalis, calcium chloride, 0.2 gm. a day, was given intravenously on 2 days; there was no increase in the volume of urine. The results were identical when the observations were repeated. The output of urine did not increase, and the patient became worse and died. An autopsy was performed. The diagnosis was: chronic cardiac valvular disease (mitral stenosis, aortic stenosis, tricuspid stenosis), verrucous endocarditis (mitral, aortic and tricuspid), septicemia (Streptococcus hemolyticus), fibrous pericarditis, fibrous pleurisy, general edema, ascites, hydrothorax, splenomegaly, infarcts of the lungs and the spleen, advanced chronic passive congestion of the organs, cirrhosis of the liver, calcification of the pancreas, fatty degeneration of the aorta, decubitus ulcers.

CASE 10.—A. B. This patient was a female, 44 years old. The diagnosis was: *Etiological:* acute rheumatic fever (inactive); *anatomical:* mitral stenosis and insufficiency, cardiac hypertrophy, right ventricular preponderance; *physiological:* normal sinus rhythm, congestive heart failure. The signs of congestive heart failure were ascites, enlargement of the liver, and edema. The patient had been the subject of chronic congestive heart failure for 20 months. During this time paracentesis had been performed every 3 weeks for relief of ascites. The first attack of failure occurred 3 years before. The usual measures were without effect in relieving the patient of edema and ascites. Calcium chloride, 0.1 gm. a day, was injected intravenously on 3 days. The output of urine did not increase. She was not benefited by the administration of digitalis, nor did diuresis occur when novasurol was given. She became worse and died. The autopsy diagnosis was: chronic cardiac valvular disease (mitral stenosis), ascites, hydropericardium, chronic passive congestion of the liver, spleen and pancreas, chronic peritonitis, perihepatitis, perisplenitis, cirrhosis of the liver.

CASE 11.—A. W. This patient was a negro, 71 years old. The diagnosis was: *Etiological:* arteriosclerosis, arterial hypertension; *anatomical:* cardiac hypertrophy, chronic myocarditis, left ventricular preponderance; *physiological:* normal sinus rhythm, congestive heart failure. The patient had suffered from two attacks of congestive heart failure. The first occurred 4 months before. The signs of congestive heart failure were right and left hydrothorax, ascites, enlargement of the liver, and edema. The Wassermann reaction of the blood was negative. The systolic blood pressure measured 223 mm. of mercury and the diastolic 134 mm.

The preliminary period before giving calcium chloride was not as well controlled as in the case of the other patients. While resting in bed the volume of urine increased. A water balance had not been reached under these conditions when calcium chloride was given. Calcium chloride, 0.2 gm., was injected intravenously on each of 4 days and 0.5 gm. on the fifth day. The volume of urine remained above the fluid intake on each of these days; the increase in output was not greater, however, than had been the fluctuations before calcium chloride was

given. At this time facial erysipelas developed and the patient died. The diagnosis at autopsy was: facial erysipelas, chronic myocarditis, fatty degeneration of the heart, cardiac hypertrophy and dilatation, hydropericardium, general arteriosclerosis, edema, ascites, hydrothorax, terminal pneumonia of the upper lobe of the right lung, anthracosis, arteriosclerotic kidneys, perisplenitis and perihepatitis, umbilical and inguinal hernias.

Summary.—In these 4 patients, then, diuresis did not occur as a result of injecting calcium chloride intravenously.

To eight patients calcium chloride was given in combination with digitalis. It was injected either before digitalis had been given, at the same time, or after the administration of digitalis.

CASE 12.—M. L. The patient was a male, 65 years old. The cardiac diagnosis was: *Etiological:* arteriosclerosis; *anatomical:* cardiac hypertrophy, chronic myocarditis, mitral insufficiency, aortic roughening, left ventricular preponderance; *physiological:* normal sinus rhythm, right intraventricular heart-block, congestive heart failure. Four attacks of congestive failure occurred in one year. The signs of failure were enlargement of the liver and edema. The patient remained in bed and was taking 1200 c.c. of fluid a day. The output of urine remained low. Calcium chloride, 0.5 gm., was injected intravenously. Increase in output did not occur. Since the patient was getting worse rapidly, digitan, 0.7 gm., was given within 9 hours. That day his output rose to 2843 c.c., and it was 5915 c.c., 3233 c.c., 2382 c.c., 1140 c.c., 1123 c.c., and 998 c.c., respectively on the succeeding 6 days. The patient lost 12.6 kg. in weight in 7 days; edema disappeared; the liver was no longer palpable. It was not necessary to give the patient more digitalis while he remained in hospital.

The observations in this patient were not satisfactorily controlled because he was acutely ill. When calcium chloride was injected intravenously one day followed by the administration of digitalis by mouth the next day, marked diuresis occurred. Several months later another attack of congestive failure occurred. On this occasion diuresis occurred when digitalis alone was given.

CASE 13.—P. P. This patient was a male, 51 years old. The cardiac diagnosis was: *Etiological:* arteriosclerosis; *anatomical:* chronic myocarditis, cardiac hypertrophy; *physiological:* auricular fibrillation, congestive heart failure. This was the first attack the patient had suffered. It had been present for one month. The signs of congestive failure were right hydrothorax, enlargement of the liver, ascites and edema. The systolic blood pressure measured 120 mm. mercury and the diastolic 80 mm. The patient was given digitalis. Moderate diuresis occurred. Two days later calcium chloride, 0.5 gm., was injected intravenously. The volume of urine diminished. Following the administration of digitan, 0.4 gm., the output increased slightly for 2 days. The increase in output was, however, no more than occurred following the administration of digitalis alone. The patient left the hospital against advice.

CASE 14.—S. C. (See Case 2, Stewart[14]). This patient was a male, 66 years old. The cardiac diagnosis was: *Etiological:* arteriosclerosis; *anatomical:* mitral insufficiency, cardiac hypertrophy, left ventricular preponderance; *physiological:* auricular fibrillation, congestive heart failure. The signs of congestive failure were pulmonary congestion and edema. The patient had suffered from 3 attacks of failure in 5 years. The Wassermann reaction of the blood was negative. The systolic blood pressure measured 140 mm. mercury and the diastolic 80 mm.

This patient was kept under the influence of digitalis for 3 weeks. He was then given calcium chloride, 0.3 gm., 0.3 gm., and 0.1 gm., respectively on 3 days.

There was no increase in the output of urine. This is the patient in whom moderate diuresis occurred when calcium chloride was given by mouth. The patient died following an attack of acute cardiac dilatation. The diagnosis at autopsy was: general arteriosclerosis, chronic cardiac valvular disease, cardiac hypertrophy, aneurysm of the abdominal aorta, diffuse hyperplastic sclerosis of the kidneys and the pancreas, infarcts of the kidneys, terminal bronchopneumonia.

CASE 15.—M. de H. This patient was a male, 72 years old. The cardiac diagnosis was: *Etiological:* arteriosclerosis; *anatomical:* cardiac hypertrophy, mitral insufficiency, chronic myocarditis, left ventricular preponderance; *physiological:* auricular fibrillation, congestive heart failure. The signs of decompensation were left hydrothorax, ascites, enlargement of the liver, and edema. The patient had suffered from two attacks of heart failure. The first occurred 4 years before. The systolic blood pressure measured 114 mm. of mercury and the diastolic 76 mm.

Calcium chloride, 0.2 gm., was injected intravenously on the same day that digitan, 0.5 gm., was given by mouth. The next day calcium chloride, 0.1 gm., and digitan, 0.2 gm., were given, and on the following day, calcium chloride, 0.1 gm. Diuresis did not occur. Later, when digitan, 2.1 gm., was given in 5 days, marked diuresis occurred, and the patient became free of the signs of congestive heart failure.

CASE 16.—D. di L. This patient was a male, 32 years old. The cardiac diagnosis was: *Etiological:* acute rheumatic fever; *anatomical:* mitral insufficiency, cardiac hypertrophy and dilatation, right ventricular preponderance; *physiological:* auricular fibrillation, congestive heart failure. The signs of failure were ascites and edema. The patient had suffered from 2 attacks of heart failure. The first occurred 3 years before.

When digitalis was given, the volume of urine increased. While moderate diuresis was occurring, calcium chloride, 0.3 gm., was injected on 2 days and 0.2 gm. on the next 2 days; the administration of digitalis was continued. A further increase in the volume of urine did not occur. During the next 2 weeks calcium chloride, 0.3 gm., was injected for several days in succession, and the administration of digitalis continued. Diuresis did not occur. The patient became worse and died. The diagnosis at autopsy was: chronic cardiac valvular disease (mitral), verrucous endocarditis (tricuspid and aortic) calcification of the mitral valve.

CASE 17.—G. B. (See Case 4, Stewart[14].) The patient was a male, 69 years old. The cardiac diagnosis was: *Etiological:* arteriosclerosis; *anatomical:* aortic stenosis and insufficiency, mitral insufficiency, cardiac hypertrophy, left ventricular preponderance; *physiological:* auricular fibrillation, congestive heart failure. The signs of congestive heart failure were right hydrothorax, enlargement of the liver, ascites and edema. This attack, the first that the patient had suffered, had been present for 6 months. Calcium chloride, 0.1 gm., 0.1 gm., and 0.2 gm., was given on 3 successive days. The volume of urine did not change. The administration of digitan, 0.5 gm., on the fifth day did not increase the output. Calcium chloride, 0.1 gm., was given on the seventh, and 0.2 gm. on the eighth days. Still it did not increase. On the day that digitan, 0.5 gm., was given a slight increase occurred. The administration of calcium chloride, 0.2 gm., on the eleventh and twelfth days, and of digitan, 0.5 gm., on the thirteenth day was not followed by diuresis. When calcium chloride and digitan were given in the same manner on the fourteenth, fifteenth and sixteenth days, increase in output again did not occur. The administration of digitalis was continued. One week later calcium chloride was given on 3 days (0.1 gm., 0.2 gm., and 0.2 gm., respectively). Diuresis did not occur. The patient died several weeks later. The diagnosis at autopsy was: general arteriosclerosis, chronic cardiac valvular disease (aortic), perforation of the intraventricular

septum, contraction of scar in the conus of the pulmonary artery, hypertrophy and dilatation of the right and left ventricles, chronic myocarditis, venous congestion of the organs, arteriosclerotic kidneys, cysts of the kidneys.

CASE 18.—S. F. (See Case 1, Stewart[14].) This patient was a female, 24 years old. The cardiac diagnosis was: *Etiological:* acute rheumatic fever (inactive); *anatomical:* mitral stenosis and insufficiency, aortic insufficiency, cardiac hypertrophy, left ventricular preponderance; *physiological:* auricular fibrillation, congestive heart failure. The patient had suffered from 3 attacks of failure. Edema was present and the liver was enlarged. She had been in hospital for many months. The administration of digitalis was followed by slight diuresis, but it was not sufficient to free the patient of edema. Calcium chloride, 0.1 gm. a day, was given intravenously on 5 days. Diuresis did not occur. On the sixth day, the administration of digitan, 0.9 gm., was not followed by a greater diuresis than had occurred on previous occasions when its administration had not been preceded by the injection of calcium chloride. The effect of digitalis was allowed to wear off. Calcium chloride, 0.1 gm. a day, was given on 6 days; increase in output did not occur. On the eighth day, digitan, 0.5 gm., was given; slight diuresis occurred. On a third occasion when calcium chloride, 0.1 gm. a day, was given for 2 days followed by digitan, 0.5 gm., a change in output likewise did not occur. On a fourth occasion, calcium chloride was given in 0.1 gm. doses on 8 days; the volume of urine did not increase. Now when on the ninth day digitan, 0.5 gm., was given, no greater output occurred than was expected from giving digitalis alone.

In short when calcium chloride was injected intravenously alone, diuresis did not occur. When the injection of calcium chloride was followed by the administration of digitalis the increase in output was no greater than occurred when digitalis was given alone.

CASE 19.—O. M. The patient was a male, 44 years old. The cardiac diagnosis was: *Etiological:* hypertension, acute rheumatic fever (13 years before), syphilis (Wassermann reaction positive); *anatomical:* mitral insufficiency, aortic insufficiency, cardiac hypertrophy, left ventricular preponderance; *physiological:* normal sinus rhythm, congestive heart failure. Four attacks of heart failure had occurred within 2 years. The signs of failure were hydrothorax, ascites and edema. The systolic blood pressure measured 190 mm. of mercury and the diastolic 60 mm. The administration of theocalcin (Merck) was followed by satisfactory diuresis. When digitan was given in doses sufficiently large to affect the form of the T-waves of the electrocardiograms, increase in the volume of urine did not occur. When the patient was no longer under the influence of digitalis, calcium chloride, 0.5 gm., was injected intravenously. The next day he was given digitan, 0.9 gm., the next day 0.4 gm., and on the following day 0.1 gm. Diuresis did not occur. The patient became free of edema after several months. This end was attained by limiting the fluid intake and by the administration of theocalcin and digitalis. While in hospital dullness on percussion and râles on auscultation appeared in the left side of the chest in front. At the same time a shadow was seen in the x-ray photograph of the chest. A diagnosis of tumor of the lung was made. It increased in size very rapidly, and the patient died of carcinomatosis two months later. The diagnosis at autopsy was: carcinomatosis of left lung, liver and lymph glands, chronic passive congestion of the left kidney; hydronephrotic contraction of the right kidney. The heart on gross examination appeared normal.

Summary.—When calcium chloride combined with the administration of digitalis was given intravenously to 8 patients suffering from congestive heart failure, diuresis did not occur except in one instance

(Case 12). In this case there is doubt whether calcium chloride played a part in inducing diuresis.

SUMMARY

As has already been stated we could obtain no evidence by the methods we employed that calcium chloride in the doses given influenced either the force or the extent of contraction of the heart. Furthermore, when it was given to 12 patients with edema a diuretic effect was not observed. Nor did diuresis occur when the injection of calcium chloride was combined with the administration of digitalis. In one patient (Case 12) in whom the observations were not satisfactorily controlled, there occurred striking diuresis when digitalis was given twenty-four hours after the injection of calcium chloride. There is reason from a later experience with this patient for thinking, however, that calcium chloride played no part in initiating diuresis. Increases in output did not occur when calcium chloride was given to patients who were not suffering from congestive heart failure.

DISCUSSION

In only one of our cases did we observe, following the intravenous injection of calcium chloride, such a striking effect as Singer reported. In this instance it is not certain that calcium chloride played a major part. In the other cases diuresis did not occur. Most of the patients were those in whom all the measures employed were without effect in removing the fluid from the subcutaneous tissues and serous cavities; in most instances progression of heart failure continued until death occurred. Two, however (Cases 8 and 15), responded readily to other drugs (digitalis, theocalcin). We did not inject doses larger than 1 gm. Salvesen, Hastings and McIntosh[15] have shown that if this amount of the salt is injected into dogs the amount of calcium in the serum of the blood increases 30 to 31 per cent shortly after injection and returns to normal four to six hours later. It may be that when this amount of calcium chloride is distributed through the much greater volume of fluid which is present in man, that it is so diluted as not to raise appreciably the level of calcium concentration of the blood.

That this amount of calcium chloride has an effect on the hearts of dogs was shown in our preliminary experiments; in these we demonstrated that 30 per cent of the calculated lethal dose of digitalis when combined with calcium chloride gave rise to ventricular premature contractions, while 25 per cent of the calculated lethal dose may be injected simultaneously with calcium chloride without the appearance of premature contractions. We observed no effect, however, on the heart when 1 gm. of the salt (calcium chloride) was given to patients, whether they were or were not under the influence of

digitalis at the time of the injection. There was no increase in the extent of left ventricular contraction, in the force of ventricular contraction and no effect on the heart muscle that could be detected electrocardiographically. If doses were given to patients comparable to those given to dogs, effects might have been detected by the methods we employed. It did not seem wise, however, to inject larger amounts, since Singer observed striking results when only 0.1 gm. of the salt was injected alone or when this amount was combined with extremely small doses of digitalis. In the one patient in our series (Case 12) in whom diuresis occurred, it is uncertain, as has already been stated, whether this result was connected with the preliminary injection of calcium chloride. On a subsequent admission excellent diuresis occurred when digitalis alone was given. From our experience with digitalis and from our present experience with calcium chloride it seems unlikely that calcium chloride played a rôle in initiating the diuresis that occurred.

CONCLUSIONS

1. Calcium chloride when injected intravenously in man in amounts as large as 1 gm. had no effect on the extent of contraction of the left ventricle (method of the moving x-ray film); it was without effect on the force of contraction of the heart (if the number of effective beats in patients suffering from auricular fibrillation is used as a criterion); and it had no effect on the electrocardiograms. These were the results whether the patient was or was not under the influence of digitalis when calcium chloride was injected.

2. The injection of calcium chloride intravenously into patients suffering from congestive heart failure in doses varying between 0.1 and 1 gm. did not result in diuresis. Digitalis did not appear to be more effective as a diuretic in these patients when it was combined with calcium chloride than when it was given alone.

REFERENCES

1. Merunowicz: Ueber die chemischen Bedingungen für die Entstehung des Herzschlages, Arbeiten a. d. physiol. Leipzig, 1875, Anstalt, p. 132.
2. Ringer, S.: A Further Contribution Regarding the Influence of the Different Constituents of the Blood on the Contraction of the Heart, J. Physiol. **4**: 29, 1883.
3. Howell, W. H.: On the Relation of the Blood to the Automaticity and Sequence of the Heartbeat, Am. J. Physiol. **2**: 47, 1898.
   Howell, W. H.: An Analysis of the Influence of Sodium, Potassium, and Calcium Salts of the Blood on the Automatic Contraction of the Heart Muscle, Am. J. Physiol. **6**: 181, 1901.
   Howell, W. H.: The Cause of the Heartbeat, J. A. M. A. **46**: 1749, 1906.
4. Loeb, J.: Ueber Ionen welche rythmische Zuckungen der Skelettmuskeln hervorrufen, Festschrift für Professor Fick, Braunschweig, 1899, p. 101.
   Loeb, J.: Ueber die Bedeutung der Ca- und K-Ionen für die Hertztätigkeit, Arch. f. d. ges. Physiol. **80**: 229, 1900.
5. Burridge, W.: Researches on the Perfused Heart: The Effects of Inorganic Salts, Quart. J. Exper. Physiol. **5**: 347, 1912.

6. Mines, G. R.: On Functional Analysis by the Action of Electrolytes, J. Physiol. **46**: 188, 1913.
7. Clark, A. J.: The Influence of Ions Upon the Action of Digitalis, Proc. Roy. Soc. Med. **5**: 181, 1912.
8. Konschegg, A. v.: Ueber Beziehungen zwischen Herzmittel- und physiologischer Kationenwirkung, Arch f. exper. Path. u. Pharmakol. **71**: 251, 1913.
9. Loewi, O.: Ueber den zusammenhang zwischen Digitalis- und Kalziumwirkung. II. Mitteilung, Arch f. exper. Path. u. Pharmakol **82**: 131, 1917.
Loewi, O.: Ueber den zusammenhang swischen Digitalis- und Kalziumwirkung. III. Mitteilung, Arch. f. exper. Path. u. Pharmakol. **83**: 366, 1918.
10. Singer, R.: Das Kalzium in der Herztherapie. Therap. Halbmonatschr. **35**: 758, 1921.
11. Hellmann, E., and Kollmann, G.: Weiterer Bericht über die kombinierte Kalzium-Digitalis-Behandlung bei Herzkranken, Therap. d. Gegenw. **65**: 444, 1924.
12. Loewenberg: L'action cardiotonique et l'action diurétique du chlorure de calcium, Ann. d. med. **13**: 172, 1923.
13. Cohn, A. E., and Stewart, H. J.: Evidence that Digitalis Influences Contraction of the Heart in Man, J. Clin. Investigation, **1**: 97, 1924,
14. Stewart, H. J.: The Oral Administration of Calcium Chloride in Congestive Heart Failure, AM. HEART J. **4**: 512, June, 1929.
15. Salvesen, H. A., and Hastings, A. B., and McIntosh, J. F.: The Effect of the Administration of Calcium Salts on the Inorganic Composition of the Blood, J. Biol. Chem. **60**: 327, 1924.

DIGITALIS TOLERANCE OF PATIENTS SUFFERING FROM RENAL INSUFFICIENCY*

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THE clinical impression has been prevalent that patients suffering from renal insufficiency do not tolerate digitalis well.[1, 2] It has been believed that patients rapidly cumulate the drug and that digitalis intoxication occurs after the administration of small doses. The present observations were undertaken to test the validity of this conception.

Ten patients diagnosed as having chronic glomerular nephritis with varying degrees of renal insufficiency were chosen as subjects for this study. All patients were in hospital, and none had received digitalis previously during the hospital admission. The diagnosis of chronic glomerular nephritis was made on the history of a chronic illness, the presence of a secondary anemia, and on the urinary findings (pale urine, fixed low gravity, containing albumin, with casts and red blood cells). All patients had impairment of renal function as indicated by the retention of protein metabolites in the blood. The laboratory data are summarized in Table I. Electrocardiograms were taken before

TABLE I

PATIENT	AGE	P. S. P. 2 HR.	UREA MG. PER 100 C.C.	TINCTURE OF DIGITALIS ALTERING T-WAVE	EQUIVALENT DOSE OF POWDER	TIME TO FIRST CHANGE OF T-WAVE	TOTAL DOSAGE	SYMPTOMS WITH DOSAGE
A. M.	20 years		268	9.3 c.c.	0.93 gm.	24 hrs.	64.0 c.c.	None
R. L.	44 "	17%	157	6.6 c.c.	0.66 gm.	16 hrs.	20.0 c.c.	Vomited 20.0 c.c.
L. B.	41 "	15%	259	8.0 c.c.	0.8 gm.	48 hrs.	14.6 c.c.	Vomited 14.6 c.c.
A. C.	28 "	15%	380	28.0 c.c.	2.8 gm.	6 days	28.0 c.c.	Vomited 28.0 c.c.
S. H.	64 "	23%	151	8.0 c.c.	0.8 gm.	2 days	26.6 c.c.	Vomited 26.6 c.c.
J. A.	49 "	35%	114	9.3 c.c.	0.93 gm.	2 days	15.3 c.c.	Vomited 15.3 c.c.
A. R.	40 "	30%	74	6.0 c.c.	0.6 gm.	2 days	21.0 c.c.	Vomited 14.6 c.c.
S. S.	47 "	7%	276	12.0 c.c.	1.2 gm.	3 days	20.0 c.c.	None
A. D.	36 "	0	341				28.0 c.c.	None
A. R.	35 "		38	12.0 c.c.	1.2 gm.	2 days	21.3 c.c.	None

digitalis was given. The usual leads were employed, and all records were taken after customary standardization of the string. (Introduction of 1 millivolt—1 cm. deflection.) Digitalis was administered as the U. S. P. tincture of known potency and in doses comparable with clinical practice, viz., 1.3 c.c. three times daily. This dosage was chosen additionally because Cohn, Fraser, and Jamieson used like

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amounts in their study of the effects of digitalis on the T-wave (0.4 gm. digipuratum daily). The results of this study then can be compared with the results of their observations. The physiological effect of the drug was noted clinically (loss of appetite, nausea, vomiting) and electrocardiographically (flattening and inversion of the T-wave).

RESULTS

Ten patients with glomerular nephritis were given 1.3 c.c. tincture of digitalis three times daily until electrocardiographic evidence of digitalization occurred or until clinical symptoms of intoxication were noted. The first definite alteration in contour of the T-wave was noted, and this early change was checked with later marked alteration in contour. From 6.6 c.c. to 12 c.c. were given before the T-wave altered. In one instance 28 c.c. were given before change in the T-wave occurred. The total amount of digitalis taken varied from 14.6 to 64 c.c. In the last column is noted the amount of digitalis which was necessary before nausea or vomiting occurred. The latter symptoms could not be observed in one case because of the presence of nausea before the administration of digitalis.

DISCUSSION

The amount of digitalis required to induce intoxication was first studied by Withering.[3] He wrote that "about thirty grains of the powder or eight ounces of the infusion may generally be taken before the nausea commences." He gave one to three grains of the powder twice daily. This observation is one in which most clinicians will concur. It will be seen in Table I (last column) that the total dosage required to cause nausea varied from 14.6 c.c. to 26.6 c.c. (21.9 to 39.9 grains). Cohn, Fraser, and Jamieson[4] noted that the T-wave in the electrocardiogram was usually inverted after the administration of digitalis. They noted also a variation in the amount of digitalis causing this change. With a usual daily dose of 0.4 gm. of digipuratum the first change in T-wave was seen as early as from 36 to 48 hours after the onset of therapy. The inversion of the T-wave in their series lasted from 5 to 22 days after the drug had been stopped. In two of our cases the T-wave returned to normal in 12 and in 20 days respectively. Bromer and Blumgart[5] recently noted a great variation in the amount of digitalis required to alter the T-wave.

CONCLUSION

It will be seen that these ten patients with impaired renal function, from moderate to considerable degree, tolerated digitalis well. The amounts of digitalis necessary to alter the T-wave in the electrocardiogram were no less than cardiac patients usually require. This observation was confirmed by clinical evidence as well.

REFERENCES

1. Sollmann, T.: A Manual of Pharmacology, Philadelphia and London, 1922, p. 483, W. B. Saunders Co.
2. Stevens, A. A.: A Textbook of Therapeutics, Philadelphia and London, 1923, p. 43, W. B. Saunders Co.
3. Withering, W.: An Account of the Foxglove and Some of Its Medical Uses, with Practical Remarks on Dropsy and Other Diseases, Birmingham, 1785, p. 182, Robinson.
4. Cohn, A. E., Fraser, F. R., and Jamieson, R. A.: The Influence of Digitalis on the T-Wave of the Electrocardiogram, J. Exper. Med. **21**: 593, 1915.
5. Bromer, A. W., and Blumgart, H. L.: The Maintenance Dose of Digitalis: An Electrocardiographic Study, J. A. M. A. **92**: 203, 1929.

THE VELOCITY OF BLOOD FLOW IN HEALTH AND DISEASE AS MEASURED BY THE EFFECT OF HISTAMINE ON THE MINUTE VESSELS*†

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INTRODUCTION

THE velocity of the blood flow is an important characteristic of the circulation.[1, 2] In different individuals under similar conditions variations are relatively slight, while in various pathological states of the circulation considerable deviations from the normal are present. The variations from the normal often parallel the degree of circulatory insufficiency. Measurement of the velocity of blood flow along the important pathways is, therefore, serviceable in evaluating objectively the efficiency of the circulation. It is of considerable practical importance that measurement of the velocity of blood flow should demand little cooperation on the part of the patient. The results of a number of methods for the measurement of various aspects of the circulation are of doubtful value because their proper application depends upon full cooperation of the patient.

All methods used in the past for the measurement of the velocity of blood flow in man consist in the injection of a relatively indifferent substance into a peripheral vein and the determination of the time elapsing between the injection and the arrival at another designated part of the vascular system. This arrival time has been determined: *A*, by the appearance of the color of the injected substance in the serum following arterial or venous punctures (fluorescein);[3] or *B*, by registration of change in the conductivity in the blood as a result of the arrival of an injected electrolyte. Concentrated salt solution has been injected intravenously, and an electrode through the skin has been inserted next to the radial artery,[4] or into the cubital vein.[5] The arrival of the salt solution in the corresponding part of the vessel has been registered with the aid of a galvanometer. *C*, a third method used for the measurement of the circulation time is that of injecting a small amount of nontoxic radio-active substance intravenously and detecting its arrival in one or several parts of the vascular system by specially constructed detectors which are sensitive enough to register the direct radiation of the active deposit when the latter arrives at the part of the vessel

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under observation.[6, 7, 8] Each of these methods offers certain advantages over the others, depending on the purpose of the inquiry.

THE PROBLEM

While engaged in a study of the effect of the intravenous administration of histamine on the peripheral part of the vascular system of normal individuals,[9] it was observed that the onset of facial flush followed the injection of histamine at a quite definite and regular interval, and that the onset of the flush was rather sharp and easily detectable. It was thought that the time interval elapsing between the injection into the antecubital vein and the appearance of the flush might express the time necessary for a particle of blood to progress from the antecubital vein into the small vessels of the face.*

Attempts to measure the circulation time with the administration of chemical substances which exert a definite effect on some easily observed physiological function are few. Loevenhart, Schmolovitz and Seybold[11] determined the circulation time of the rabbit and the cat by injecting sodium cyanide intravenously. Sodium cyanide, as is well known, stimulates the respiratory center, and so the period elapsing between the injection and the appearance of increased respiration was used as a measure of the circulation time. The circulation time obtained by this method in rabbits corresponded closely to that obtained with ferrocyanide, hexamethylene tetramine and lithium chloride. In cats the reaction time to sodium cyanide was slower than the circulation time obtained by the other methods.

Bornstein[12] administered one deep breathful of air containing between 5 and 7 per cent of carbon dioxide to normal subjects and to patients, and the time interval between the inhalation of the carbon dioxide and the appearance of the first deep inspiration was used as an expression of the circulation time between the capillaries of the lung and of the respiratory center. Bornstein recognized that this method was inaccurate and that its application was greatly limited by the variability in the response of the respiratory center to carbon dioxide in many pathological conditions. According to him, the circulation time observed under such experimental conditions was about half of the cubital vein to cubital vein circulation time. As far as we know, only short preliminary reports appeared on these two attempts.

The application of a chemical substance which exerts a definite and easily detectable change on a bodily function offers the great advantage for the measurement of the circulation time because of its extreme simplicity. To use a substance for such a purpose the following prerequisites should be fulfilled:

1. The substance must not be toxic in the amounts utilized.

*Harmer and Harris[10] administered intravenously small amounts of histamine in a few instances.

2. The substance should not influence the velocity of the blood flow during the first circuit of its flow following the injection.

3. The substance and its effect on the body should disappear rapidly, so that the test can be repeated at short intervals.

4. The reaction time of the substance after its arrival in the tissues where the proper changes are expected should be short.

5. The change in the function of the body which is used as a signal of the arrival of the substance should occur both in normal and in pathological conditions of the body, and should be detected easily.

The time which elapses between the injection of a substance and the detection of the signal sign (flush, respiratory effect, etc.) includes the circulation time, and also the time necessary for the effect of the chemical agent to manifest itself following the arrival of the substance in the small blood vessels (capillaries). This latter period (the time elapsing between the arrival of the substance into the capillaries and the manifestation of its action) should be called the reaction time proper of a substance. This reaction time is more uniform than the "reaction time" which includes the entire period from the time of injection until the manifestation of the physiological change. Nevertheless, hereafter the term reaction time is used as the time which elapses between the injection of histamine and the onset of flush as observed.

PLAN OF INVESTIGATION

The intensity of the pharmacodynamic effect of a substance depends on the concentration in which it comes into contact with the tissues. It was expected, and found by experience, that the smaller the volume and the greater the concentration of the histamine solution injected, the more definite and intense was the facial flush. The injection of a small volume also had the advantage of not changing the blood volume in any appreciable amount. The application of histamine in increased concentration was limited by its undesirable effect on the body. After the administration of relatively large doses, a marked rise in the cardiac rate, occasional marked fall in the blood pressure, sensation of weakness, headaches, nausea and vomiting were observed. After some experience it was found that the sudden injection of 0.001 mg. of histamine phosphate per kilogram of body weight in a concentration of 1:10,000 or 1:5000 regularly produced marked flush of the face in white individuals. Almost simultaneously with the onset of flush, a sensation described as "salty," "metallic," "electric" is felt in the tongue of the subject. This sensation offers a check for the observation of the color. In the later part of our investigation we used the concentration of 1:5000 of a solution of histamine phosphate, 0.35 c.c. being used in an average man of 70 kg.* The injection was made suddenly

*All doses are expressed in terms of histamine phosphate.

from a finely graduated Luer syringe. The time of the injection and the onset of flush and taste were registered with a stop watch. Good direct daylight facilitated the recognition of the flush.

To ascertain whether the time obtained under such an experimental condition corresponded to the true circulation time, and to gather evidence as to whether the procedure was feasible for practical application, the following observations were made.

The reaction times of a large number of normal subjects and of patients were studied, and the results were compared with the circulation time obtained on another group by the radioactive deposit method. To compare the results of the two procedures in the same individual under identical conditions, the histamine reaction time and the circulation time by the radioactive deposit method were determined simultaneously in normal persons and in patients with cardiovascular disease. To ascertain whether the histamine circulation time could be repeated at short intervals, tests were made on the same individuals at short intervals. To observe the effect of the intravenously administered histamine on the circulation, the cardiac rate was measured by electrocardiographic tracings taken during and after the measurement of the circulation time. Similarly repeated blood pressure determinations were carried out during and after the test. As the pharmacodynamic action of histamine produces marked effects on the small vessels, it was important to learn whether the drug exerted any definite effect on the pulmonary arterioles, capillaries and venules. If such an effect were present, it might alter the circulation, the very thing to be measured. Direct observations on the effect of histamine on the pulmonary capillaries of man are not feasible. For this reason direct observations were made on the pulmonary capillaries in the cat.[13] No definite changes were observed in the behavior of the pulmonary capillaries. In addition, the pulmonary circulation time of normal subjects and of patients was measured following the injection of histamine.

OBSERVATIONS

The Reaction Time of Histamine in Normal Individuals.—Histamine phosphate, in amounts of 0.001 mg. per kg. of body weight in 1:5000 or 1:10,000 solution, was injected into the antecubital vein of 65 normal subjects, and the reaction time on the small vessels of the face was determined. The ages of these individuals varied from fourteen to sixty-nine years. All tests were performed with the subjects in the recumbent position after their confidence and cooperation had been obtained. The findings are summarized in Table I, according to the age incidence of the subjects. In 65 normal subjects the reaction time between the cubital vein and the small vessels of the face varied between 13 and 30 seconds; the average circulation time was 23 seconds. It is of interest that the arm to arm circulation time in 53 normal individu-

als measured by the radium active deposit method, varied between 14 and 24 seconds; the average circulation time was 18 seconds.[8] The slightly more prolonged reaction time obtained by the histamine method is probably explained by the fact that the histamine method measures the time necessary for the arrival of the blood to the capillaries, while the radioactive deposit method measures the time of arrival of the blood in a large artery (cubital artery). It is known that the blood flow slows down considerably in the smaller vessels. E. Hering[14] estimated the capillary circulation time to be 5 seconds. Koch[3] observed in one subject the appearance of fluorescein in the cubital artery in 10 seconds, while the dye was detected in the cubital vein in 18 seconds, corresponding to a capillary circulation time of 8 seconds. We observed even greater difference between the arterial and venous circulation times with the fluorescein method.[8] The time

TABLE I

THE REACTION TIME OF HISTAMINE IN SIXTY-FIVE NORMAL INDIVIDUALS

AGE	NO. OF SUBJECTS	AVERAGE HEART RATE	AVERAGE BLOOD PRESSURE SYSTOLIC	AVERAGE BLOOD PRESSURE DIASTOLIC	REACTION TIME MINIMAL	REACTION TIME MAXIMAL	AVERAGE
Years			mm. Hg.	mm. Hg.	seconds	seconds	seconds
10-19	12	82	118	64	13	22	18
20-29	16	80	116	72	14	30	21
30-39	13	84	124	76	15	29	23
40-49	10	78	128	80	20	30	25
50-59	7	80	134	84	17	22	20
60-69	7	84	138	88	21	27	25

which elapses between the arrival of histamine in the small facial vessels and the appearance of flush, may also be a factor in the difference between the results obtained with the two methods. It should be remembered, however, that the two procedures applied measure the circulation time between two different parts of the body which may be different even when measured with the same method.

With the onset of the flush there was a subjective sensation of heat over the face and tension in the head which lasted from 1 to 3 minutes. There was a period of from 15 to 30 seconds after the onset during which the flush increased in intensity. The flush was localized over the face and neck, the rest of the body showing a flush in but few instances. The total duration of the flush was from 12 seconds to 2 minutes. With the onset of flush the cardiac rate increased. The duration of increased cardiac rate, as a rule, went parallel with the duration of flush. Its height was reached in about 15 to 60 seconds after the onset of the flush. The maximum rise in the heart rate was from 15 to 20 beats a minute. Blood pressure, as a rule, showed but little change during and after the flush. A definite fall was not obtained. A slight rise of 10 to 20, mm. Hg., in the systolic and diastolic pressures, during and immedi-

ately after the flush, was observed frequently. With the return of the cardiac rate to normal the blood pressure likewise became normal again. A number of patients complained of throbbing headaches which began 10 to 20 seconds after the onset of the flush and lasted usually from 3 to 10 minutes.

The Relation of the Onset of the Increased Heart Rate to the Onset of Flush.—The intravenous injection of histamine in the amounts described was always followed by an elevation of cardiac rate. In order that the histamine reaction may be used for the measurement of the velocity of blood flow, it is essential that the very characteristics of the circulation to be measured should not change. Although change in the heart rate does not necessarily imply change in the velocity of blood flow, it is desirable that the increase of the cardiac rate should not occur before the onset of flush. Numerous observations indicated that the onset of increased cardiac rate was coincident with the onset of flush and sensation of taste. In order to study this aspect of the problem in a more exact way, the cardiac rate of normal subjects and patients suffering from circulatory failure was registered continuously by Lead II of the electrocardiographic machine. At the moment of injection and at the appearance of flush the string of the galvanometer was temporarily short circuited. The cardiac rate was registered 30 to 60 seconds after the onset of flush. The analysis of the records indicates that in 8 of 14 observations acceleration of the cardiac rate was increased with or immediately after the onset of flush. In 6 observations there was a slight increase in rate by 2 and 3 seconds before the onset of flush. It is of interest that a number of subjects showed temporary inversion of the T-wave for from 20 to 60 seconds. This inversion of the T-wave with the acceleration disappeared as the rate returned to normal.

The observation that with the increase of rate there was a depression of the T-wave suggests that the increase of rate is the result of the effect of histamine on the coronary vessels of the heart and that this increase of rate begins simultaneously with the flush, or 2 to 3 seconds before it is noted.

Repeated Tests in the Same Individuals.—Repeated tests were performed on a number of individuals to ascertain the difference in repeated measurements, and to determine how soon the test could be repeated. The flush, changes in heart rate and in blood pressure suggested that the persistence of the effect of a single intravenous dose of histamine is of short duration, and that the test could be repeated within a few minutes. Observations substantiated this expectation. Table II presents a few of our findings in normal individuals and in patients.

The average variations were not more than 2 to 3 seconds. The findings presented in Table II indicate that the test can be repeated within 5 and in some cases even within 3 minutes. In patients with circulatory failure, especially when this is due to myocardial degeneration

TABLE II

REPEATED ESTIMATION OF THE REACTION TIME OF HISTAMINE IN THE SAME PERSON

DATE	NAME	AGE	CONDITION	PULSE	HIST. PH. PER KG. OF BODY WEIGHT	REACTION TIME	TIME INTERVAL BETWEEN REPETITION OF TESTS	DIFFERENCE BETWEEN REACTION TIMES
1928		(years)			mg.	Sec.	Min.	Sec.
4-4	T. D.	24	Diabetes	70	0.0010	20	9	0
				78		20		
4-4	T. M.	19	Bronchitis	68	0.0011	17	12	1
				76	0.0011	16		
4-4	T. G.	18	Normal	72	0.0011	18	3	1
				72	0.0011	17		
4-5	N. F.	48	Normal	78	0.0003	23	11	0
				76	0.0008	23		
				80	0.0012	24	6	1
				76	0.0015	24	3	1
				72	0.0017	23	3	0
5-22	A. K.	28	Post. Pneum.	74	0.0007	35	13	6
				72	0.0010	29		
4-5	P. R.	63	Emphysema	63	0.0008	26	7	2
					0.0011	24		
6-16	R. M.	41	Arterial hypertension	84	0.0010	28	3	2
				86	0.0010	30		
4-21	H. T.	45	Aortic insufficiency	96	0.0009	29	6	1
				104	0.0009	28		
4-7	S. S.	75	Arteriosclerosis	96	0.0009	37	13	3
				92	0.0007	40		
4-13	J. F.	75	Myocardial degeneration	110	0.0005	45	7	4
			Auricular fibrillation	104	0.0008	49		
5-5	P. M.	54	Myocardial degeneration	100	0.0011	59	11	17
				100	0.0011	42		
5-10	L. E.	56	Myocardial degeneration	72	0.0011	64	9	7
				88	0.0008	57		

and arteriosclerosis, the variations were considerably higher. The duration of the flush, as well as the change in heart rate and subjective sensation, lasted longer in these patients than in normal individuals. We believe that this greater variation in the results is due, at least partly, to fluctuations in the velocity of blood flow. In patients with circulatory failure it is advisable not to repeat the test within 10 minutes. As the observation on patient N. F. indicates, the amount of histamine can vary considerably without change in the circulation time. The minimal effective dose is about three times smaller than the dose usually applied.

Simultaneous Measurement of the Histamine Reaction Time and the Circulation Time by the Radioactive Method.—The measurements described indicated that the histamine reaction time in normal individuals corresponds closely to the arm to arm circulation time, as measured with the radioactive deposit method. For a more definite establishment of the significance of the histamine reaction time, simultaneous measurements with the two methods were performed both on normal individuals and on patients suffering from cardiovascular disease. For this purpose the amount of radioactive deposit required for the measurement of the circulation time and the histamine were dissolved

TABLE III

COMPARISON OF CIRCULATION TIMES AS DETERMINED BY THE RADIUM AND HISTAMINE METHODS IN NORMAL INDIVIDUALS

NO.	NAME	CIRCULATION TIME (RADIUM)			CIRCULATION TIME (HISTAMINE)		DIFERENCE HISTAMINE CIRC. TIME	DIFERENCE RADIUM CIRC. TIME
		ARM TO HEART	PULMONARY	ARM TO ARM	ARM TO FACE (FLUSH)	ARM TO TONGUE (TASTE)	FLUSH AND ARM TO ARM	TASTE AND ARM TO ARM
		sec.	sec.	sec.	sec.	sec.	sec.	sec.
528	T. C.	4.5	20.0	24.5	22	23	−2.5	−1.5
537	F. T.	5.5	11.0	16.5	20	22	+3.5	+5.0
535	J. K.	4.0	7.0	11.0	15	14	+4.0	+3.0
529	W. G.	6.0	10.0	16.0	21	20	+5.0	+4.0
531	G. McG.	6.0	11.0	17.0	23	21	+6.0	+4.0
524	W. C.	6.0	11.0	17.0	22	—	+5.0	——
536	R. P.	11.0	13.5	24.5	31	31	+6.5	+6.5
530	T. Mc.	4.0	9.5	13.5	20	21	+6.5	+7.5
533	D. L.	3.5	7.5	11.0	19	17	+8.0	+6.0
534	W. S.	3.5	9.0	12.5	21	21	+8.5	+8.5
	Average	5.4	11.4	16.4	21.4	21.1	+5.0	+4.7

in the same solution. The concentration of the histamine was less in these tests than usually used. Both the venous blood flow to the right side of the heart and the pulmonary circulation time were measured with the radioactive deposit method. Table III represents the comparative findings on ten normal subjects. Table IV is the summary of the results obtained on eight patients with cardiovascular disease. In addition to the reaction time of histamine on the facial vessels, both tables include the reaction time on the small vessels of the tongue, as determined by the sensation of metallic taste. The two reaction times of histamine, as a rule, do not differ more than 1 or 2 seconds in normal individuals. The flush may become visible slightly before or after the sensation of taste. As indicated by Tables III and IV, the histamine reaction time is always longer than the arm to arm circulation time. The average arm to arm circulation time in the ten normal individuals was 16.4 seconds, and the average histamine reaction time was 21.4 seconds. The average histamine reaction time, just as observed before,

TABLE IV

COMPARISON OF CIRCULATION TIMES AS DETERMINED BY THE RADIUM AND HISTAMINE METHODS IN CARDIAC PATIENTS

NO.	NAME	AGE	DIAGNOSIS	HEART RATE	ART. PRESS. SYST.	ART. PRESS. DIAST.	VEN. PRESS.	VIT. CAP.	CIRCULATION TIME (RADIUM) ARM TO HEART	CIRCULATION TIME (RADIUM) PULMONARY	CIRCULATION TIME (RADIUM) ARM TO ARM	CIRCULATION TIME (HISTAMINE) ARM TO FACE (FLUSH)	CIRCULATION TIME (HISTAMINE) ARM TO TONGUE (TASTE)	DIFFERENCE HIST. CIRC. TIME FLUSH AND ARM TO ARM	DIFFERENCE RAD. CIRC. TIME TASTE AND ARM TO ARM
		Years		per min.	mm. Hg.	mm. Hg.	mm. H_2O	c.c.	sec.	sec.	sec.	sec.	sec.	sec.	sec.
546	P. M.	66	Myocardial degeneration	56	135	80	−15	2400	–	–	41.0	44	–	+ 3.0	–
547	J. G.	60	Arteriosclerosis	100	138	82	+10	2800	15.0	16.0	31.0	37	39	+ 6.0	+8.0
552	J. W.	55	Myocardial degeneration	80	156	56	+10	3000	12.0	25.5	37.5	44	46	+ 6.5	+8.5
542	E. C.	56	Decompensated hypertension	72	126	82	–	3200	25.0	27.0	5.1	60	–	+ 8.0	–
539	W. N.	42	Auricular fibrillation; Myocardial degeneration	80	130	80	−10	3700	7.0	14.0	21.0	30	–	9.0	–
544	J. S.	65	Myocardial degeneration	70	96	58	−10	2800	7.0	12.0	19.0	31	27	+12.0	+8.0
551	J. G.	62	Myocardial degeneration	100	118	70	+10	1700	13.0	21.0	34.0	47	–	+13.0	–
543	J. J.	68	Arterial hypertension	70	220	108	+20	3700	6.0	14.0	20.0	34	–	+14.0	–
						Average			12.1	18.5	31.9	40.9	37.3	+ 9.0	+8.2

is 5 seconds slower than the average arm to arm circulation time. The average arm to arm circulation time of the seven patients with cardiovascular disease was 31.9 seconds; the average histamine reaction time was 40.9 seconds. The histamine reaction time, therefore, was 9 seconds longer than the arm to arm circulation time. This relatively greater difference between the two methods in patients with circulatory failure is not unexpected for the histamine reaction time includes the circulation time of the small vessels, in which the velocity of blood flow is proportionately slow. The difference between the histamine and arm to arm circulation times of normal individuals and that of patients with circulatory failure is about the same when the difference is expressed in percentage of the reaction time. The observations suggest that the reaction time of histamine corresponds to the circulation time as closely as under the conditions of observation one may expect. The findings also indicate that the small vessels of the face react very promptly to the action of histamine after it reaches the capillaries. The reaction time of histamine bears such constant relationship to the arm to arm circulation time that the former can be used for the estimation of the velocity of blood flow in man.

After it became established that normal subjects and cardiac patients exhibit a reaction time with histamine which corresponds closely to the circulation time of the same region of the body, we undertook the estimation of the reaction time of patients suffering from various pathological conditions.

The Reaction Time of Histamine in Patients with Cardiovascular Disease.—The patients observed were divided into two groups, according to whether or not they were suffering from symptoms and signs of decompensation at rest at the time of performance of the test. Table V presents some of the findings on patients suffering from cardiovascular disease other than arterial hypertension, without symptoms and signs of congestive failure. Table VI presents the findings on patients with symptoms and signs of congestive failure. In 13 patients suffering from cardiovascular disease without symptoms and signs of circulatory failure, the histamine reaction time varied from 17 to 35 seconds; the average reaction time was 25 seconds. This corresponds to the average circulation time of 24 seconds found with the radioactive test in cardiac patients who showed no symptoms or signs of decompensation at the time when the observations were made.[15, 16] The average vital capacity of 9 patients was 3183 c.c. or 1928 c.c. per meter of body surface. With the exception of patient H. R., the reaction time of all the patients was within normal limits, although the average reaction time was slightly greater than that of the normal individuals studied. This finding is again in harmony with the observations made with the radioactive deposit method, that cardiac patients without symptoms and signs of circulatory failure may have a normal circulation time, and the

TABLE V

THE REACTION TIME OF HISTAMINE IN PATIENTS SUFFERING FROM CARDIOVASCULAR DISEASE, BUT WITH NO EVIDENCE OF CIRCULATORY FAILURE

NAME	AGE	DIAGNOSIS	PULSE	ARTERIAL BLOOD PRESSURE SYSTOLIC	DIASTOLIC	VITAL CAPACITY	VITAL CAPACITY PER SQ. METER	HISTAMINE PH. INJECTION	REACTION TIME
	Years			mm. Hg.	mm. Hg.	c.c.	c.c.	mg. per Kg.	seconds
T. C.	14	Rheumatic heart disease; Mitral stenosis	88	120	56	3800	2400	0.0011	17
B. N.	34	Myocardial degeneration; Auricular fibrillation	56	140	70	–	–	0.0010	20
E. S.	15	Rheumatic heart disease; Auricular fibrillation	92	110	50	–	–	0.0008	20
J. W.	55	Syphilitic heart disease; Aortitis and aortic insufficiency	84	140	52	3450	1875	0.0012	21
J. W.	55	Syphilitic heart disease; Aortic insufficiency	84	140	52	3450	–	0.0010	22
I. M.	32	Rheumatic heart disease; Mitral stenosis and insufficiency	76	140	92	–	1895	0.0012	21
I. R.	21	Rheumatic heart disease; Aortic insufficiency and mitral stenosis	72	122	44	3800	2290	0.0011	25
M. C.	23	Rheumatic heart disease; Mitral stenosis and insufficiency	72	126	74	2750	1870	0.0011	25
C. D.	48	Rheumatic heart disease; Auricular fibrillation	68	130	72	4100	2350	0.0013	26
A. C.	20	Acute rheumatic fever; Mitral stenosis	92	–	–	3000	2200	0.0011	26
E. T.	60	Arteriosclerosis; Myocardial degeneration	72	140	90	2550	1510	0.0011	29
A. W.	72	Arteriosclerosis; Myocardial degeneration	82	154	76	–	–	0.0011	30
D. S.	58	Arteriosclerosis; Myocardial degeneration	72	156	100	1800	948	0.0012	30
H. R.	62	Myocardial degeneration; Auricular fibrillation	72	128	60	3400	1910	0.0012	35

vital capacity of these patients may be slightly reduced.[15] Three of the four patients who showed fibrillation of the auricles showed reaction times within normal limits. This finding indicates, as observed before, that the velocity of blood flow may be normal with total irregularity of the heart beat if the function of the myocardium is good. Patient C. D. was an intelligent window washer who served in the Spanish-American War in 1898 and was then diagnosed as suffering from completely irregular pulse. After having a cardiac irregularity for over 30 years he walks with ease up 14 flights of stairs without stopping. He was admitted to the hospital on account of a minor surgical condition. The general reaction of these patients to histamine was the same as that of normal subjects. Only one of the patients complained of severe headache which lasted 10 minutes.

The reaction time of histamine in patients with symptoms and signs of congestive failure at time of test varied from 21 to 82 seconds. The average reaction time was 47 seconds. The average arm to arm circulation time of similar patients observed with the radioactive deposit method was 38 seconds. The average difference between the histamine reaction time of normal subjects and that of patients with circulatory failure was approximately 100 per cent. The same difference was found with the radioactive deposit method. The average vital capacity of patients was 1807 c.c., or 1007 c.c. when reduced to the value for a square meter of body surface. This average vital capacity was lower than that of patients with signs of circulatory failure in whom the circulation time was measured with the radioactive deposit method.

The lower vital capacity is due partly to the fact that a relatively larger number of patients observed by the histamine method suffered from severe congestive failure than those observed before with the radioactive deposit method. This is also indicated by the fact that eleven out of the twenty-six patients died, in spite of treatment, within three months after the performance of the test. The average reaction time of the 11 patients who died in the hospital as a result of circulatory failure was 50 seconds. This average reaction time of the patients who died from circulatory failure was not appreciably longer than that of patients who improved, or whose condition remained unaltered. We, therefore, did not observe a critical reaction time with prognostic significance. As indicated in Table VI, the prolongation of the reaction time was not necessarily proportional to the severity of the clinical condition, though a markedly prolonged circulation time was always associated with severe circulatory failure. It is of special interest in connection with this statement that patient M. L., on whom repeated tests were performed 8 hours before his death, had a reaction time of only 28 and 29 seconds. This patient was suffering from syphilitic heart disease and paroxysmal dyspnea (cardiac asthma) of one month's duration. He was admitted to the hospital 24 hours before his death

TABLE VI

THE HISTAMINE REACTION TIME IN PATIENTS WITH CIRCULATORY FAILURE

NAME	AGE	HEART RATE	ARTERIAL BLOOD PRESSURE SYSTOLIC	ARTERIAL BLOOD PRESSURE DIASTOLIC	VITAL CAPACITY	VITAL CAPACITY PER SQ. METER	HISTAMINE PH INJECTION	REACTION TIME	DIAGNOSIS AND REMARKS
	(Years)	per min.	mm. Hg.	mm. Hg.	c.c.	c.c.	mg. per Kg.	seconds	
M. L.	45	104	170	50	–	–	0.0009	28	Syphilitic heart disease with aortic insufficiency. Died as result of pulmonary edema 8 hours later.
M. L.	45	100	164	48	–	–	0.0009	29	
J. M.	44	150	–	–	1000	525	0.0009	33	Myocardial degeneration; auricular fibrillation; anasarca.
J. R.	61	70	145	95	2800	1400	0.0008	34	Coronary sclerosis and cardiac infarct five months previously. Weakness, no edema or other signs of congestive failure.
J. R.	61	70	145	90	2800	1400	0.0006	45	
G. M.	60	92	208	106	1650	970	0.0010	35	Myocardial degeneration; arterial hypertension; dyspnea; slight dependent edema.
C. H. S.	±60	108	160	114	–	–	0.0012	35	Myocardial degeneration; auricular fibrillation; dyspnea.
W. M.	65	68	160	60	1800	975	0.0011	35	Myocardial degeneration; arteriosclerosis; moderate dependent edema; Cheyne-Stokes breathing.
R. C.	65	60	126	65	1700	870	0.0010	35	Myocardial degeneration; arteriosclerosis; auricular fibrillation; dyspnea; emphysema.
R. C.	65	60	118	60	1700	870	0.0008	38	
J. W.	55	112	163	60	2650	1160	0.0009	36	Syphilitic heart disease; aortic insufficiency; orthopnea; dependent edema.
B. O'L.	75	96	190	130	1500	800	0.0009	37	Arteriosclerosis; myocardial insufficiency; orthopnea; dependent edema.
B. O'L.	75	92	190	130	1500	800	0.0009	40	
W. W.	64	64	170	80	2900	1810	0.0011	37	Myocardial degeneration; moderate dyspnea.
C. H. S.	±60	100	–	–	1800	1130	0.0011	42	Myocardial degeneration; arteriosclerosis; Cheyne-Stokes breathing.
C. H. S.	±60	100	156	124	1800	1130	0.0011	59	
T. W.	75	60	–	–	2700	1380	0.0011	43	Myocardial degeneration; arteriosclerosis; emphysema; dyspnea; dependent edema.

TABLE VI—CONT'D

NAME	AGE	HEART RATE	ARTERIAL BLOOD PRESSURE SYSTOLIC	ARTERIAL BLOOD PRESSURE DIASTOLIC	VITAL CAPACITY	VITAL CAPACITY PER SQ. METER	HISTAMINE PH INJECTION	REACTION TIME	DIAGNOSIS AND REMARKS
	(Years)	per min.	mm. Hg.	mm. Hg.	c.c.	c.c.	mg. per Kg.	seconds	
M. J.	75	110	–	–	–	–	0.0005	45	Myocardial degeneration; auricular fibrillation; emphysema; dyspnea; slight dependent edema.
M. J.	75	–	–	–	–	–	0.0008	49	
J. B.	47	48	204	114	1350	740	0.0011	45	Syphilitic heart disease; aortic insufficiency; arterial hypertension; orthopnea; marked dependent edema.
D. P.	61	110	–	–	1800	1020	0.0008	49	Myocardial degeneration; auricular fibrillation; orthopnea; edema.
P. D. M.	68	76	220	112	2150	1180	0.0008	49	Myocardial degeneration; arterial hypertension; orthopnea; dependent edema.
F. G.	74	96	216	106	1000	575	0.0010	50	Myocardial degeneration; emphysema, dyspnea; edema; arterial hypertension.
D. McN.	56	68	116	84	2000	1040	0.0011	50	Myocardial degeneration; auricular fibrillation; cardiac paroxysmal dyspnea; orthopnea.
D. McN.	56	76	110	84	2000	1040	0.0008	62	
D. McN.	56	68	108	86	2000	1040	0.0006	82	
W. P.	55	64	–	–	1300	690	0.0009	53	Rheumatic heart disease; auricular fibrillation; anasarca.
W. P.	55	62	–	–	1300	690	0.0009	55	
T. V.	69	74	152	90	1050	525	0.0010	56	Myocardial degeneration; orthopnea; edema.
D. McN.	56				2200	1150	0.0008	57	Myocardial degeneration; auricular fibrillation; cardiac paroxysmal dyspnea; orthopnea.
D. McN.	56				2200	1150	0.0006	58	
D. McN.	56	72	114	92	2200	1150	0.0011	64	
A. L. P.	75	80	178	60	800	480	0.0013	57	Aortic insufficiency; anasarca; syphilitic heart disease.
A. L. P.	75	84	162	58	–	–	0.0013	58	
D. R.	66	76	130	42	1600	850	0.0010	60	Syphilitic heart disease; aortic insufficiency; dyspnea, anasarca.
C. H. S.	±60	–	–	–	–	–	0.0012	67	Myocardial degeneration.
C. H. S.	±60	108	–	–	–	–	0.0012	70	

with symptoms and signs of acute pulmonary edema. Prompt venesection and strophanthin intravenously improved the patient's condition, and he felt comfortable. The next day he suffered from a similar attack, from which, despite treatment, he did not recover. Postmortem examination revealed syphilitic aortitis with aortic insufficiency, vegetative endocarditis, right hydrothorax, pulmonary edema and ascites. The clinical behavior and autopsy findings in this patient indicated that the death was due to sudden failure of the left side of the heart. It is suspected clinically that a slight disproportion between the function of the two sides of the heart may be of grave consequence. It is obvious that in such a type of failure, the velocity of blood flow is not necessarily prolonged, and in the explanation of the death other factors than change in velocity must play more important rôles. In patients with myocardial degeneration the prolongation of circulation time is more apt to be proportionate to the severity of clinical condition than in patients with valvular disease. This is illustrated by patient C. H. S., who, as his condition grew worse, exhibited a continually increasing reaction time (35, 42, 59, 67, 70 seconds).

It was noted during these observations that several patients with signs of congestive failure exhibited more marked unpleasant reactions to the injections of histamine than normal subjects or patients without symptoms and signs of congestive failure. In patients with circulatory failure following the injection of histamine the flush was often more intense and of longer duration than in normal subjects. This prolonged and marked flush was especially intense in patients who, in addition to the myocardial degeneration, exhibited clinical evidence of emphysema of the senile type. In patient T. W., for example, who had shown definite evidence of emphysema including an inspiratory restriction of the lower ribs (Hoover's sign), there was a flush of the face which lasted for 6 minutes following the intravenous injection of 0.001 mg. of histamine per kg. We have never observed in normal subjects a flush of such long duration following a single similar intravenous dose. It is of great interest that 10 of the patients of this group, in contrast to normal subjects and to the other group of patients with cardiovascular disease, without evidence of decompensation, developed dyspnea of 2 to 3 minutes' duration. The type of dyspnea varied. In some of the patients it was predominantly expiratory and wheezing. Three patients, prior to the administration of histamine, showed a low diaphragm which moved but slightly under the fluoroscope, and an inspiratory restriction of the lower ribs (Hoover's sign). After histamine they developed a temporarily accentuated Hoover's sign. We are unable to state with certainty whether the restriction of the diaphragm was the result of associated emphysema or whether it was caused by the dyspnea as a result of the circulatory failure, for we believe that an inspiratory restriction of the lower ribs can be caused

by other types of dyspnea than that due to emphysema. Several of the patients who developed dyspnea of short duration after histamine have shown no evidence of emphysema, but they have suffered previously from paroxysmal nocturnal dyspnea (cardiac asthma). One of the patients who showed the most marked reaction following the administration of histamine was a young man (R. R.) 30 years old, who was suffering from rheumatic heart disease with signs of aortic insufficiency and mitral stenosis. He was given an intravenous injection of 0.0008 mg. of histamine phosphate per kg. About 14 to 20 seconds after injection there was a gradually increasing dyspnea, and the patient had to sit up. There was both inspiratory and expiratory difficulty. The dyspnea lasted for 5 minutes. When 0.2 c.c. of epinephrin of 1:3000 was given by vein, the patient received instant relief. The vital capacity changed from 3500 c.c. to 1500 c.c. even shortly after the dyspnea was relieved. The lowered vital capacity gradually became normal after the administration of adrenalin. It is of interest that this patient was readmitted two months later because of severe attacks of nocturnal dyspnea. This patient showed an increased sensitivity to histamine. Histamine in this and in other cardiac patients produced dyspnea similar to that observed in patients with acute bronchitis, asthma and pulmonary emphysema. That dyspnea in these patients with cardiovascular disease was not due to peripheral dilatation of the vessels is shown by the fact that the change in blood pressure was not more marked than in other patients without dyspnea. But the most weighty evidence against the dyspnea being of peripheral origin is the observation that in a number of patients the dyspnea started at about the half period of the histamine reaction time. In these patients it is probable that the dyspnea was due to sensitivity of the pulmonary structures to histamine. The fact that adrenalin relieved the dyspnea favors the conception that the dyspnea in these cases was due to the sensitivity of the smooth muscles of the bronchioles to histamine. Whether in other patients in whom the dyspnea started after the elapse of the reaction time, peripheral dilatation of the coronary or other vessels played a rôle cannot be stated with any certainty. The test should not be applied in patients with evidence of coronary disease. In order to avoid unpleasant reactions in patients with myocardial degeneration and dyspnea small doses of 0.005 mg. were given first and only when no reaction to such a dose was noted was the amount increased.

The Histamine Reaction Time in Patients With Arterial Hypertension.—This group of patients, with the exception of patients I. M. and S. Z., were ambulatory and were living a normal life. With the exception of these two patients all had subjective complaints only. All the ambulatory patients showed reaction times which were within the limits of normal. The two patients who exhibited a prolonged reaction time were hospitalized, and in addition to the hypertension they exhib-

ited symptoms and signs of marked cardiovascular changes. The findings presented in Table VII are again in harmony with the observations made before,[16] that the velocity of blood flow is within the limits of normal or slightly prolonged in patients with arterial hypertension but without circulatory failure. The average blood pressure was 187/118 mm. The average circulation time was 26 seconds. The average circulation time of the nine patients who were ambulatory and able to attend work was 23 seconds, which is the average circulation time observed in normal subjects.

The Histamine Reaction Time in Patients With Pulmonary Emphysema.—The six patients studied in this group suffered from such severe weakness and dyspnea that they were confined to bed. Chronic bronchitis and attacks of bronchial asthma were etiological factors in the production of the emphysema. The severity of the respiratory disturbance was so marked that four of the patients have shown marked cya-

TABLE VII

THE HISTAMINE REACTION TIME OF PATIENTS WITH ARTERIAL HYPERTENSION

NAME	AGE	HEART RATE	ARTERIAL BLOOD PRESSURE		HISTAMINE INJECTED	REACTION TIME
			SYSTOLIC	DIASTOLIC		
	Years	per min.	mm. Hg.	mm. Hg.	mg. per Kg.	seconds
S. M.	40	76	174	110	0.0006	17
V. H.	45	100	210	130	0.0005	19
F. L.	50	88	188	114	0.0009	20
F. G.	35	96	170	104	0.0006	20
F. G.	35	96	164	104	0.0004	26
B. L.	59	84	190	130	0.0010	21
J. G.	56	104	210	138	0.0012	21
J. G.	56	108	210	140	0.0010	22
J. G.	56	108	190	132	0.0012	22
J. G.	56	104	168	126	0.0012	23
J. G.	56	92	150	108	0.0012	24
H. D.	65	80	194	108	0.0011	26
H. D.	65	84	182	100	0.0006	26
M. F.	64	96	190	98	0.0011	26
M. F.	64	96	206	100	0.0008	31
A. T.	41	84	215	125	0.0010	28
A. T.	41	80	225	135	0.0010	30
J. M.	60	80	–	–	0.0011	36
S. X.	71	104	180	120	0.0006	40

nosis over the face and mucous membranes. All patients exhibited, in addition to the signs described in Table VIII, a low diaphragm with slight excursion, hyperresonant percussion notes, obliteration of the cardiac dullness, and numerous rhonchi and râles. As indicated in Table VIII, the reaction times were well within the limits of normal, with the exception of patient Th. W. The average reaction time was 26.4, slightly above the average of normal reaction times. If we exclude the last patient, who showed marked prolongation in the blood flow, the average reaction time is 24 seconds. In these patients with

TABLE VIII

THE HISTAMINE REACTION TIME IN PATIENTS WITH MARKED PULMONARY EMPHYSEMA

NAME	AGE	HEART RATE	VITAL CAPACITY	VITAL CAPACITY PER SQ. METER	HISTAMINE MG. PER KG.	REACTION TIME	REMARKS
	Years	per min.	c.c.	c.c.		seconds	
P. R.	±65	78	2000	1038	0.0012	18	Cough and attacks of asthma for 17 years. Marked dyspnea. Unable to walk but few steps. Marked cyanosis. Positive Hoover's and other signs of emphysema.
P. R.	±65	76	2000	1038	0.0008	24	
J. H.	53	100	1350	798	0.0009	24	Chronic cough for 30 years. Marked dyspnea with cyanosis. Unable to work. Able to walk on level but slowly. Physical signs of emphysema.
M. G.	63	70	3100	1480	0.0010	24	Chronic cough and productive expectoration for 20 years. Shortness of breath at slightest exertion. Comfortable at rest. Cyanosis, barrel-shaped chest and other signs of emphysema. Severe arteriosclerosis. Auricular fibrillation.
M. G.	63	68	3100	1480	0.0007	26	
C. W.	66	60	1125	635	0.0006	25	Chronic cough and frequent attacks of asthma for 17 years. Cyanosis and other signs of emphysema.
C. W.	66	64	1200	640	0.0006	23	
E. B.	74	90	1100	749	0.0007	27	Cough and dyspnea of many years duration. Unable to walk but short distance. Clinical signs of emphysema and of arterial hypertension.
Th. W.	75	60	——	——	0.0010	43	Cough of years duration. Dyspnea, signs of emphysema, including Hoover's sign.
Th. W.	75	60	2700	1380	0.0006	—	

pulmonary emphysema, therefore, although the vital capacities per square meter of body surface were approximately the same as those of patients with extreme severe circulatory failure, the velocity of blood flow was within normal limits. The physical disability in these patients was due, therefore, primarily to the failure of the respiratory function of the lungs. In emphysema with complete disability, the velocity of blood flow through the lungs, as observed before, may be normal. In some instances decrease in the velocity of blood flow may occur if there is also cardiac failure. The significance of the normal velocity of blood flow in patients with pulmonary emphysema was pointed out in a previous communication.[17]

All patients with emphysema, bronchitis and bronchial asthma showed temporarily increased dyspnea with the appearance of symptoms and signs of bronchial asthma after the administration of histamine. The dyspnea was transient. It was also noted that patients with emphysema exhibited an unusually prolonged facial flush.

The Histamine Reaction Time in Patients With Clinical Evidence of Hyperthyroidism.—The rapid heart rate, the warm skin, the results of direct capillary observation, the high basal metabolism, all suggest that the velocity of blood flow is rapid in patients with increased thyroid secretion. Liljestrand and Stenström[18] found an increased minute volume output of the heart in patients suffering from hyperthyroidism. Table IX presents a correlation between the pulse rate and the rate of

TABLE IX

THE HISTAMINE REACTION TIME IN PATIENTS WITH HYPERTHYROIDISM

NAME	AGE	HEART RATE PER MIN.	REACTION TIME
	Years		Seconds
M. C.	23	104	9
E. B.	32	124	9
J. H.	36	120	11
J. H.	36	134	12
W. F.	38	94	No reaction
W. F.	38	—	15
W. F.	38	—	16
W. F.	38	79	15
J. H.	36	132	19
J. H.	36	128	22
D. H.	54	108	24
D. H.	54	108	27

the metabolism and histamine reaction time. As expected, the velocity of blood flow was increased in all the patients except in patient D. H. The average reaction time was 16.3 seconds, which is 29 per cent lower than the average circulation time of 23 seconds in normal subjects. The increased velocity of 29 per cent corresponds closely to the average rise of 35 per cent in the basal metabolism. A correlation between the increase in cardiac rate, basal metabolism, and reaction time was not present in a given patient.

The duration of flush was short. Otherwise, the reaction of the patients to histamine was the same as that of normal subjects.

The Histamine Reaction Time in Patients With Pernicious Anemia.—It was expected that the determination of the histamine reaction time by the appearance of the flush might be difficult in patients with marked anemia. It was found that several patients with a severe degree of primary anemia showed no definite flush from histamine. Several of these patients could indicate the reaction time from the sudden appearance of metallic taste in the tongue. We could not establish a definite level of hemoglobin or red cell count below which the flush cannot be determined, and it is possible that the reaction of the capillaries and other small vessels may be altered in pernicious anemia. This possibility is suggested by the fact that at times the appearance of slight facial flush may be the earliest indication of the approaching remission, and it may appear without any increase, or even with a decrease, in the hemoglobin or red cell content of the blood.

Seven patients, in whom we succeeded in determining the histamine reaction time, both by flush and by the appearance of taste in the tongue, are presented in Table X. The average hemoglobin content of

TABLE X

THE REACTION TIME IN PATIENTS WITH PERNICIOUS ANEMIA

NAME	AGE	HEART RATE PER MIN.	RED BLOOD CELLS IN MILLIONS	REACTION TIME
	Years			Seconds
S. L.	58	104	2.40	9
J. F.	53	84	—	10
F. N.	64	68	3.20	10
M. A.	55	92	1.34	11
H. O'N.	70	84	3.46	15
K. M.	60	96	1.19	16
P. C.	63	80	1.79	10

the blood was 38 per cent, that of the red cell content 2.23 millions, and the average reaction time 11.5 seconds. The average velocity of blood flow was twice as rapid as in normal individuals. The increase in velocity of blood flow is proportional to the decrease of red cell count and hemoglobin.

The Histamine Reaction Time of the Human Brain Vessels.—The circulation time of different parts of the body may be different. In animals the circulation time of different organs was measured by G. N. Stewart.[19] In man it was shown by us that the circulation time of the small vessels of the upper arm and elbow is approximately the same as that of the face and tongue. During a study of the effect of histamine on the small vessels of the human body,[9m] it was observed that following the sudden intravenous injection of small amounts of histamine the intraspinal pressure showed a sudden rise which lasted between 1 and

3 minutes. In two patients suffering from brain tumor it was also observed during operative exposure of the brain that 0.001 mg. per kg. of histamine caused a flushing of the surface of the brain. With the onset of this flush the volume of the brain showed slight increase and a marked increase in the pulsation. All of these changes lasted about 90 seconds. From these and other observations previously reported, it was considered that the small vessels of the brain were very sensitive to histamine. The period which elapsed between the injection and onset of a rise of pressure indicated at once that this must correspond to the circulation time from the arm to the brain. In a group of patients suffering from various neurological conditions, in whom the performance of spinal fluid pressure determination was necessary from a diagnostic or therapeutic point of view, a small dose of histamine (0.001 mg. per kg. or less) was injected. A small glass manometer was connected with the spinal needle, and the movement of onset of the rise in spinal pressure was determined. (It is essential that fluid should not be lost previously to the injection of histamine.) The time of onset of the rise was then compared with the time of the onset of flush which was noted by another observer. Table XI shows the findings in subjects in whom the histamine reaction time from the right elbow to the face and to the brain respectively was measured simulta-

TABLE XI

COMPARISON OF THE HISTAMINE REACTION TIME FROM ARM TO FACE AND ARM TO BRAIN

NAME	AGE	DIAGNOSIS	HEART RATE PER MIN.	BLOOD PRESSURE SYSTOLIC	BLOOD PRESSURE DIASTOLIC	ARM TO FACE REACTION TIME	ARM TO BRAIN REACTION TIME
	Years			mm. Hg.	mm. Hg.	Seconds	Seconds
P. D.	19	Epilepsy	110	114	84	13	12
M. Cr.	22	Syphilis	112	110	84	15	15
R. S.	57	Cervical rib	84	100	64	17	16
E. S.	53	Alcoholic neuritis	80	140	90	16	17
			84	132	88	19	18
C. K.	18	Multiple sclerosis	90	120	65	19	17
O. B.	24	Epilepsy	68	108	78	18	19
N. J.	52	Epilepsy	100	120	90	20	20
			90	116	78	18	19
C. L.	53	Syphilis	76	136	76	21	21
R. B.	30	Chronic encephalitis	80	126	80	26	26

neously. In the patients presented in Table XI, as well as in many others, it was striking to observe how closely the reaction time of the face and vessels of the brain corresponded. The maximum difference was not more than two seconds. The average reaction time of the brain and that of the face of the same individual under identical conditions was 18 seconds. From the foregoing it is evident that the circulation times of the brain and of the face are identical. The average reaction

time in these patients was shorter than that of those included in Table I. The difference is probably due to the fact that the patients were excited as a result of the performance of spinal puncture.

An Attempt to Estimate the Velocity of the Arterial and Venous Blood Flow Separately.—An attempt was made to estimate the arterial and the venous portions of the circulation between the elbow and face by determining the histamine reaction time of normal subjects and allowing the same individuals to inhale deeply and rapidly a single breathful of amyl nitrite vapor through a small rubber cone. The time between the end of the inhalation and the appearance of flush should correspond to the time necessary for a particle of blood to travel from the pulmonary capillary through the pulmonary artery and through the arteries after leaving the heart. The distance of these arterial vessels corresponds to the distance travelled from the elbow to the capillaries through the venous vessels. It was found, however, that a number of subjects do not respond with as marked and easily recognizable a flush to amyl nitrite as they do to histamine. In the few subjects in whom definite reactions were obtained, the time was about half of that obtained with histamine, and about the same as reported by Bornstein[12] following the inhalation of carbon dioxide. Assuming that the diffusion of amyl nitrite is instantaneous through the pulmonary capillaries, it would follow that the circulation time of the arterial (pulmonary vein and peripheral arteries) and venous portions (peripheral vein and pulmonary artery) is about the same. In analogy with the knowledge of the relative diameters of the aorta and vena cava and the respective velocity of blood flow in them it would follow that in the pulmonary vein the blood flow velocity must be twice as slow as in the pulmonary artery. As the reaction to amyl nitrite was not definite in a larger number of subjects, the problem was not considered as settled.

DISCUSSION

In outlining the problem of this investigation it was stated that in order to be applicable to man, the histamine method should fulfill a number of requirements. In light of our experience histamine fulfills these prerequisites in the following way:

1. During observations on over 200 patients, no serious effects were observed. In a number of patients who suffered from circulatory failure with emphysema, bronchial asthma and bronchitis, attacks of dyspnea were precipitated. It was observed that the respiratory mechanisms of these patients were hypersensitive to the effect of histamine, and, therefore, in later observations the first dose injected was half of the usual dose. Only if unpleasant side effects were not observed after the small dose, was the second, larger, dose administered. Several of the patients studied complained of pulsating headache and a sensation of weakness of a few minutes' duration.

2. Histamine does not influence appreciably the velocity of blood flow during the first circuit of the blood, following the injection. This is supported by the finding that the acceleration of the pulse starts just before or after the appearance of the flush. That histamine does not increase the velocity of blood flow before the appearance of flush is supported by the finding that the histamine reaction time is slightly longer than the circulation time.

3. Repeated tests on the same person, as well as disappearance of the histamine effect, indicate that its effect in the body lasts but a short time, and therefore the test can be repeated at short intervals.

4. The close correspondence between the circulation time and the histamine reaction time also indicates that the minute vessels dilate promptly after the arrival of the histamine.

5. The appearance of the flush is definite enough to make it possible to estimate the circulation time of normal subjects, and patients with varied pathological conditions.

Comparing our experiences with the histamine, the radioactive, and the dye methods for the estimation of the velocity of blood flow in man, we feel that the histamine method offers certain advantages, especially in so far as its use in the clinic is concerned, over the other methods. The advantages of the histamine method over the radioactive deposit method are as follows:

1. Its use is simple, requiring no complicated apparatus and technic. With slight skill it can be performed by anybody with the aid of a stop watch.

2. The expense of the test is minimal, and histamine is easily available.

3. The test can be repeated every five to ten minutes, while the radioactive method, on account of the persistence of activity, can be repeated only at three-hour intervals.

4. The test can be performed at the bedside, while in the radioactive method the patient has to be moved to the instrument.

The disadvantages of the method as compared with the radioactive method are as follows:

1. The radioactive method is objective and more exact. It makes possible the measurement of the velocity of blood flow of several areas of the body simultaneously, including important circulatory areas (pulmonary circuit), the circulation time of which cannot be measured with histamine.

2. Short unpleasant reactions observed occasionally after the administration of histamine are not present after the intravenous administration of radioactive deposit.

3. In colored and anemic people the histamine test cannot be applied.

In comparing the histamine method with the dye methods, we feel that the histamine method is more exact, the technic simpler and less

disturbing to the patient. Furthermore, it can be performed by one person.

The use of the intravenous administration of histamine for the estimation of the velocity of blood flow serves a useful clinical purpose if it is applied with care and the results are interpreted with proper critique. The variation of the results is not greater than may be expected from the best biological methods which are influenced by similar variables. Much significance should not be attached to slight variations in the circulation time of the same or of different patients. Marked variations in the circulation time are of special practical significance in the differentiation of myocardial insufficiency from emphysema, on the one hand, and circulatory insufficiency from nephritis with edema, on the other. In such patients the estimation of the

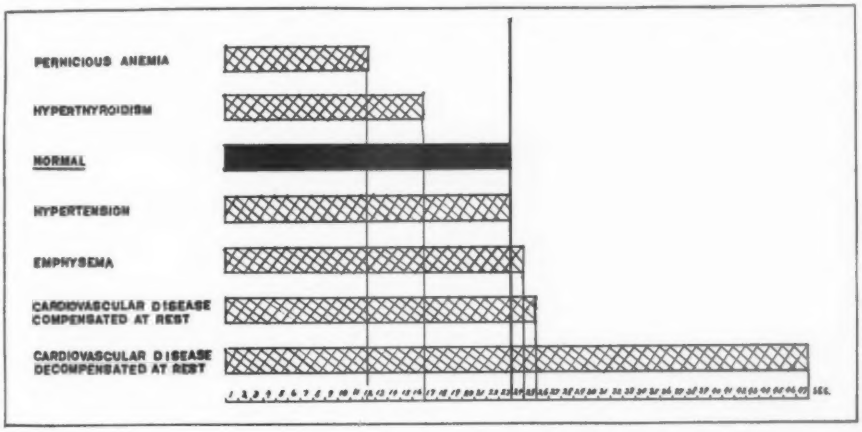

Fig. 1.—The histamine reaction time in health and in disease.

velocity of blood flow with histamine is a useful aid in the clinical evaluation of the condition.

In addition to the vessels of the face, it has been shown that the vessels of the human brain are sensitive to the action of histamine. As a result of the intravenous injection of histamine, flushing of the surface of the brain due to dilatation of the minute vessels occurs. Coincident with this flush there is a swelling and increased pulsation of the brain, and the cerebrospinal fluid pressure shows a steep rise. The rise reaches its maximum within 15 to 40 seconds, and similarly to the facial flush, reaches the normal level within three minutes. A very close relationship has been found between the time of onset of the flush and the rise in intracranial pressure. The procedure, therefore, makes it possible for the first time to estimate the velocity of blood flow from an arbitrarily chosen point to the small vessels of the brain.

An attempt was made to separate the circulation time of the venous and arterial blood from elbow to face. The amyl nitrite inhalation, as

well as the observation of Bornstein with CO_2 inhalation, indicates that the time from the capillaries of the lung to the face is about the same, or slightly less than that from the elbow to the pulmonary capillaries. As anatomical and physiological considerations indicate that the velocity in the large peripheral veins is about half that of the large peripheral arteries, it follows that the velocity of the blood flow in the pulmonary artery is also about twice that of the vein. It was observed previously that average circulation time of the peripheral venous flow is 6.7 seconds; the pulmonary circulation time 6.5 seconds; the actual loss of time in the heart is 1 to 2 seconds; the arm to arm arterial circulation time is 18 seconds; the arm to capillary circulation time is 23 seconds. It follows from these data, that the capillary circulation time is 5 seconds, the circulation time of the pulmonary artery 2.1 seconds, and that of the pulmonary vein 4.2 seconds.

The average prolongation of the velocity of blood flow in patients with symptoms and signs of circulatory failure was about 100 per cent above the average normal velocity. A number of patients with severe myocardial failure have shown a prolongation of over 200 per cent above the average normal circulation time. While in patients with myocardial failure without valvular damage the more prolonged circulation time was associated with severe circulatory failure, no definite prognostic value can be attached to the circulation time. The average circulation time of 11 patients who died as a result of severe circulatory failure was not markedly different from that of the other group of 15 patients who either recovered or were unimproved three months after the test. Occasionally severe derangement of the circulation may be present with normal or only slightly prolonged circulation time. Such a condition may exist when slight disproportion between the function of the two sides of the heart is present, a condition which occurs probably more frequently than is now recognized. In luetic aortic insufficiency the myocardium of the left ventricle may fail functionally as a result of fatigue, while the intact musculature of the right chambers continues to throw blood into the lung. That such a condition may soon lead to serious consequences is evident.

The fact that circulation time may be of value in differentiating ventilatory and circulatory insufficiency, is of great significance, for the two conditions have many common characteristics, and they offer great differential diagnostic difficulty. This difficulty becomes even greater because pulmonary emphysema and circulatory failure may often be present in the same individual. In such patients the simultaneous measurements of several characteristics of the circulation, such as of the vital capacity, circulation time and venous pressure, will be a useful aid in the estimation of the two conditions.

Patients with hyperthyroidism and severe primary anemia have shown considerable increase in the velocity of blood flow. The increase

was especially marked in patients with pernicious anemia. In patients with hyperthyroidism no definite relationship was observed by this method in the individual cases between the velocity of blood flow and the rise in basal metabolism.

We attach significance to the observation that small amounts of histamine may precipitate an attack of dyspnea of short duration in patients with bronchitis, bronchial asthma, and emphysema, as well as in certain patients with severe myocardial failure who suffer from typical attacks of cardiac asthma. The observation of the identical reaction in patients suffering from two diseases suggests that the mechanism of paroxysmal cardiac dyspnea, at least in one group of cardiac patients, may be similar to the dyspnea of bronchial asthma in which it is recognized that the bronchial musculature is sensitive to histamine. The suspicion that in a group of people with myocardial damage the changed state of the bronchial muscles, or the disturbed mechanism of the histamine plays a rôle in the precipitation of attacks of dyspnea may be understood in the light of recent knowledge on the fate and rôle of histamine in the body.[20]

SUMMARY AND CONCLUSIONS

1. The intravenous administration of histamine phosphate in amounts of 0.001 mg. or less per kg. of body weight in solution of 1:5000, or 1:10,000, causes a dilatation of the minute vessels of the face and of the brain with regularity.

2. The reaction time of histamine between the site of intravenous injection and the vessels of the face and brain can be estimated with an average variation of two seconds.

3. Estimation of the histamine reaction time in normal subjects and in patients with various pathological conditions simultaneously with determination of the circulation time by the radioactive method indicates that the histamine reaction time is a measure of the velocity of blood flow.

4. The observations reported in this study confirm the conclusions previously expressed on the significance of the circulation time in health and disease, as measured by the radioactive method.

5. In 65 normal subjects the histamine reaction time varied between 13 and 30 seconds, the average reaction time being 23 seconds between the antecubital vein and the small vessels of the face.

6. In 11 normal subjects the histamine reaction time between the cubital vein and the small vessels of the brain varied between 12 seconds and 26 seconds, the average reaction time being 18 seconds.

7. (a) It was again observed that in compensated cardiac patients the velocity of the blood flow may be within limits of normal, while in patients with symptoms and signs of circulatory failure a prolongation of over 200 per cent may be present.

(b) In patients with circulatory failure the circulation time varied between 21 and 82 seconds, with an average of 47 seconds.

(c) The average histamine reaction time of 11 patients who as a result of circulatory failure died within 3 months following the test was 50 seconds, as contrasted with 45 seconds, the average reaction time of patients with severe circulatory decompensation who either improved or showed no change within three months after the test.

(d) In failure of the left ventricle associated with pulmonary edema, such as occurs in diseases of the aorta, signs of severe circulatory failure may be present with normal or only slightly prolonged circulation time.

(e) In a group of patients with cardiovascular disease but with no symptoms and signs of circulatory failure at rest and moderate exercise, the velocity of blood flow was normal, but the vital capacity was slightly reduced. This fall in the vital capacity before the slowing of the velocity of blood flow, confirms the conception expressed before, that in progressive circulatory failure the pulmonary vascular bed may show change before there is a detectable change in the velocity of blood flow, and that the slowing of the velocity of blood flow precedes the rise in the venous pressure. During progressive improvement of the circulation the change in these characteristics of the circulation is reversed.

8. A markedly prolonged circulation time was always associated with severe circulatory failure, but the reverse was not always true. Changes in the velocity of blood flow do not necessarily have prognostic significance.

9. It was shown again that the velocity of blood flow in patients with essential arterial hypertension, but without circulatory failure, and in emphysema, is normal.

10. In anemia and hyperthyroidism the velocity of blood flow is considerably increased. The average velocity in a group of patients with hyperthyroidism was proportionate with the average increase in basal metabolism, but a similar relationship in individual cases was not always observed.

11. Among the pathological conditions studied, the velocity of the blood flow was most increased in pernicious anemia (double of the normal rate), and the decrease was greatest in severe circulatory failure (half of the normal rate). The difference between the velocity of blood flow in a given case of pernicious anemia and a severe circulatory failure was ninefold.

12. Patients with bronchitis, bronchial asthma, pulmonary emphysema and severe myocardial failure may show temporary dyspnea associated with signs of bronchial spasm following the intravenous administration of histamine. In these cases the test should be applied cautiously; half of the dose (0.0005 mg. per kg.) should be given intra-

venously slowly (5 seconds) as a test dose before the usually applied dose is given.

13. The measurement of the velocity of blood flow is an important diagnostic aid in differentiating certain diseases associated with dyspnea and edema (circulatory failure and respiratory failure; nephritis and circulatory failure).

REFERENCES

1. Blumgart, Hermann L., and Weiss, Soma: Studies on the Velocity of Blood Flow. V. The Physiological and Pathological Significance of the Velocity of Blood Flow, J. Clin. Investigation **4**: 199, 1927.
2. Blumgart, Hermann L., and Weiss, Soma: Clinical Studies on the Velocity of Blood Flow. X. The Relation Between the Velocity of Blood Flow, the Venous Pressure and the Vital Capacity of the Lungs in Fifty Patients With Cardiovascular Disease Compared With Similar Measurements in Fifty Normal Persons, J. Clin. Investigation **5**: 379, 1928.
3. Koch, E.: Die Stromgeschwindigkeit des Blutes, Deutsch. Arch. f. klin. Med. **140**: 39, 1922.
4. Meldolesi, G.: Bull. e. atti. della Reale Academica med. di Rome **52**: 267, 1925-1926.
5. Koch, E.: Die Bestimmung der Kreislaufzeit des Blutes, Handb. d. biol. Arbeitsmethoden **5**: 345, 1928.
6. Blumgart, Hermann L., and Weiss, Soma: Studies on the Velocity of Blood Flow. VI. The Method of Collecting the Active Deposit of Radium and Its Preparation for Intravenous Injection, J. Clin. Investigation **4**: 389, 1927.
7. Blumgart, Hermann L., and Weiss, Soma: Studies on the Velocity of Blood Flow. VII. The Pulmonary Circulation Time in Normal Resting Individuals, J. Clin. Investigation **4**: 399, 1927.
8. Blumgart, Hermann L., and Weiss, Soma: Studies on the Velocity of Blood Flow. II. The Velocity of Blood Flow in Normal Resting Individuals, and a Critique of the Method Used, J. Clin. Investigation **4**: 15, 1927.
9. Weiss, Soma, and Robb, George P.: Unpublished study.
9a. Weiss, Soma, Lennox, W. G., and Robb, G. P.: The Dilator Effect of Histamine on the Cerebral Vessels in Man, Proc. Soc. Exp. Med. **24**: 706, 1929.
10. Harmer, I. M., and Harris, K. E.: Observations on the Vascular Reactions in Man in Response to Histamine, Heart **13**: 381, 1926.
11. Loevenhart, A. S., Schmolovitz, B. J., and Seybold, E. G.: The Determination of the Circulation Time in Animals and Man, J. Pharmacol. and Exper. Therap. **15**: 246, 1920.
12. Bornstein, A.: Ueber die Messung der Kreislaufzeit in der Klinik., Behandlungen des Kongresses für Innere Medizin **29**: 457, 1912.
13. Wearn, J. T., Ernstene, A. C., and Bromer, A. W.: Personal Communication.
14. Hering, E.: Quoted by Koch (3), Archiv f. Phys. Heilkunde **12**: 112, 1853.
15. Blumgart, Hermann L., and Weiss, Soma: Studies on the Velocity of Blood Flow. III. The Velocity of Blood Flow and Its Relation to Other Aspects of the Circulation in Patients With Rheumatic and Syphilitic Heart Disease, J. Clin. Investigation **4**: 149, 1927.
16. Blumgart, Hermann L., and Weiss, Soma: Studies on the Velocity of Blood Flow. IV. The Velocity of Blood Flow and Its Relation to Other Aspects of the Circulation in Patients With Arteriosclerosis and in Patients With Arterial Hypertension, J. Clin. Investigation **4**: 173, 1927.
17. Weiss, Soma, and Blumgart, Hermann L.: Studies on the Velocity of Blood Flow. VIII. The Velocity of Blood Flow and Its Relation to Other Aspects of the Circulation in Patients With Pulmonary Emphysema, J. Clin. Investigation **4**: 555, 1927.
18. Liljestrand, G., and Stenström, N.: Work of Heart During Rest; Blood Flow and Blood Pressure in Exophthalmic Goiter, Acta med. Scandinav. **63**: 99, 1925.
19. Stewart, G. N.: Researches on the Circulation Time of the Spleen, Kidney, Intestine, Heart and Retina With Some Further Observations of the Lesser Circulation, Am. J. Physiol., **58**: 278, 1921.
20. Best, C. H., Dale, H. H., Dudley, H. W., and Thorpe, W. V.: The Nature of the Vasodilator Constituents of Certain Tissue Extracts, J. Physiol. **62**: 397, 1927.

DISTORTION OF THE BRONCHI BY LEFT AURICULAR ENLARGEMENT*

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THE effects of the enlargement of the left auricle on the structures of the mediastinum, which follow upon long-standing mitral disease have been known for a long time, and have been repeatedly demonstrated; but the value of detailed x-ray and fluoroscopic study in all cases suggestive of mitral disease does not seem sufficiently well realized. There are three separate items worthy of investigation: the study of the outline of the enlarged chamber itself, the study of esophageal displacement, and the study of bronchial displacement.

The anatomical localization of the left auricle and its proper relationship to other structures within the chest is the most important factor in the explanation of the phenomena following its enlargement. Jaffe[1] and Groedel[2] have investigated the position of the auricle by x-rays and anatomical dissection, and Stoerk[3] has reviewed the anatomy in the cadaver, bringing forward new points and emphasizing the important features of the relation of the bronchi and esophagus to the left auricle.

First of all the left auricle is the uppermost chamber of the heart and lies almost directly posterior. Just above it is the bifurcation of the trachea; indeed, the left main bronchus normally rests upon it for a short distance. The esophagus passes behind the left auricle and is contiguous with the pericardium overlying it for a distance of several centimeters of its course.

Since the auricle lies posteriorly instead of on the left side of the heart as its appellation designates, it may enlarge as well to the right as to the left, and its proximity to the main bronchi and the esophagus should easily lead to disarrangement of these structures in the course of enlargement.

Enlargement of the auricle to the right was first brought to notice by a report of Owen and Fenton[4] in 1901. In this case there was such massive dullness to the right of the midline that pleural effusion was diagnosed, but thoracentesis in the right axillary line yielded bright red blood, following which cardiac murmurs over the dullness were noted. At post-mortem examination it was proved that the dullness was due to a huge left auricle presenting on the right side.

Other cases of such enormous dilatation of the left auricle have been reported by Emmanuel[5] who describes several older cases from the

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London hospitals, Shaw,[6] Schott,[7] East,[8] Lutembacher[9] and others. Quite recently Bedford[10] has reviewed the subject and added two more cases, and Bramwell and Duguid[11] have established a much more sound pathological explanation of the cause than former observers, namely, fibrosis of the auricular wall.

These enormous dilatations are rare and, hence, not of common interest. A more moderate degree of dilatation, however, commonly occurs and quite frequently is apparent as a part of the right border of the heart in the roentgenogram. From the anatomical studies of Stoerk and the more recent reiteration of Neumann[12] and Assman[13] it is easily understood why the left auricle appears on the right. Neumann interprets the double curve on the right occasionally appearing in mitral stenosis as being made up of the two auricles, the left above, the right below. He also adds that this is seen rarely in cases of aortic insufficiency or arteriosclerosis with left-sided hypertrophy before much enlargement of the right side has taken place. The appearance of the left auricle on the right in such conditions, he believes, is in part due to the rotation of the heart, bringing the left auricle out from behind as in a right oblique view.

In 1922, Bordet[14] in a series of 200 unselected cases of mitral disease noted the appearance of the left auricle on the right side ten times in the outline by x-ray, yet in all of these the auricle was only moderately dilated, and no physical signs were found which might have given a clue to the condition.

In Schott's[7] six cases the auricle was somewhat more prominent, and several presented paravertebral dullness on the right side. This, however, might have been due to small amounts of fluid.

Clinically, then, definite signs of right-sided enlargement of the left auricle are only obtained when the dilatation is relatively enormous, and even then may readily be mistaken for pleural effusion or aneurysm. There may be dullness to the right of the midline extending even as far as the axillary line and murmurs may be heard over this area. Pulsations, visible and palpable, have been reported. It is also of clinical interest that in all of these cases with dilatation of the left auricle to the right in which the clinical findings were stated, auricular fibrillation was also present. This we find occurs in the two cases included in our present report.

The proximity of the esophagus to the auricle was appreciated by Joachim[15] in 1905 and Minkowski[16] in 1906 when they used it as a point from which registration of the presystolic (auricular) impulse was readily obtained. Eichorst[17] states that cardiac hypertrophy may cause compression of the esophagus, but Kovacz and Stoerk[18] were among the first observers to emphasize deviation and compression of the esophagus in enlargement of the left auricle. They injected the esophagus with a soft mass and, on removal of the specimen, demon-

strated three depressions; the uppermost from the bifurcation of the trachea and the left main bronchus, a second from the aorta, and below these a long smooth depression from the left auricle in cases with enlargement of this organ.

They then examined cases of mitral disease by x-ray while the patient swallowed bismuth suspensions or capsules and showed that the esophagus was displaced to the right and backward. The degree of displacement, they thought, was directly proportional to that of cardiac enlargement. In one case a capsule remained just above the compressed area for fifteen minutes which also indicated some obstruction.

Faulkenhausen[19] reported a case of arteriosclerotic heart disease, where compression of the esophagus occurred at two points. The first was at the level of the widened aortic arch; the second at the level of the left auricle which cavity was apparently enlarged, probably due to a functional regurgitation from the hypertrophied left ventricle.

Gabert[20] concludes that the left auricle is almost the sole factor causing compression and displacement of the esophagus, but that its enlargement may very well be part of a general left-sided hypertrophy from causes other than primary mitral disease. The latter condition, however, is responsible most frequently. Gabert also recorded the deviation posteriorly and to the right as former observers had demonstrated.

Rösler and Weiss[21] differ from others in their report, in that the esophagus deviates to the left in some of their cases. Their report deals with seven cases of mitral lesions, four of which were combined with aortic disease. They attributed the displacement to enlargement of the left auricle in all cases and explained the deviation to the left by rotation of the heart which dragged the esophagus, in its passage through the diaphragm, from its normal position just to the right of the midline, over to the left side. This must assume rotation posteriorly from right to left, anteriorly, from left to right, which is in an opposite direction from that found by most observers and contradicts Neumann's observation, that rotation was a factor in aiding the appearance of the left auricle on the right side.

The clinical significance of compression and displacement of the esophagus in patients with enlargement of the left auricle lies in the fact that these patients occasionally have difficulty in swallowing. Two of the patients reported by Rösler and Weiss complained of dysphagia, as did some of the patients in Notkin's[22] report. In the case recorded by Owen and Fenton,[4] previously mentioned, difficulty in swallowing was a prominent symptom and is, of course, frequent in the experience of many.

The development of recognition of compression of the left main bronchus has already been summarized[23] in connection with a detailed clinical report of the first case of this series. Such compression was

first reported by King[24] in 1838. Four cases, three of mitral disease, and one a congenital lesion, were shown at autopsy to have a materially decreased lumen of the left main bronchus resulting from pressure from the enlarged left auricle. Friedreich[25] first clinically diagnosed such a case in 1850 by the lung signs at the left base, the diagnosis being confirmed four years later at necropsy by Virchow. Another case was added by Taylor[26] in 1889 in an autopsy report. There are but few textbooks[27] which mention it, and until Stoerk's[3] admirable anatomical study of the normal relations and those in mitral disease, it received almost no attention. Stoerk combined the measurements of the normal angles at which the bronchi leave the trachea, of Aeby,[28] von Hovorka and Kobler[29] with his own and gave the limits of variation as in Table I (A). The values found in his eight cases of mitral disease are given in Table I (B). It is to be seen that the lower limit in mitral disease corresponds to the upper limit of normal as regards total angle. The case which furnished the minimal total angle (78°) in the series of mitral disease, presented an angle of 61° for the left bronchus. The angle of the left bronchus was, therefore, 12° more than that in any of the normal cases, the small total angle being due to the unusually slight deviation of the right bronchus, namely 17°. The greatest difference, as would be expected, is noted in the angle which the left bronchus makes with the axis of the trachea. This study was carried out on autopsy material.

Two years later, Kahler[30] by bronchoscopic examination of patients with mitral disease from Kovacz' clinic, was the first to demonstrate displacement of the left main bronchus in living subjects and showed that some compression was present in all but one of the thirteen cases, the narrowing of the lumen occasionally being extreme. In only one of these cases were there signs of pathological nature noted at the left lung base.

Quite recently Gabert[31] in x-ray studies of the heart was able to visualize the main bronchi in anteroposterior and lateral views. The comparison of his cases of mitral disease with the normal leaves no doubt that spreading of the angle of departure of the main bronchi from the trachea occurs with an enlarged left auricle. That the elevation pertains especially to the left main bronchus was in accord with former observers.

It appears that it is only in the small minority of cases, those with extreme compression of the left bronchus, that clinical signs become manifest. Usually the phenomenon has been found at autopsy or by special examination without a previous clinical diagnosis. The physical signs appear only when secondary lung changes take place, such as atelectasis, or chronic infection and bronchiectasis which require rather marked obstruction for their production. Then we find persistent moisture, stridulous respiration, and even dullness with breath sounds

which may vary from a diminished vesicular murmur to loud tubular breathing. They may be coupled with long continued fever, cough, and expectoration of sputum. Such signs have occurred in the past, but only once, and that three-quarters of a century ago, has a diagnosis been made on that basis. This was made by Friedreich[25] in 1850.

X-RAY STUDY

The Outline of the Auricle.—

The examination is made both fluoroscopically and roentgenologically, the patient being examined in the anteroposterior position, in both oblique positions and in the lateral position. In the right oblique position the right breast is against the film or screen; in the left

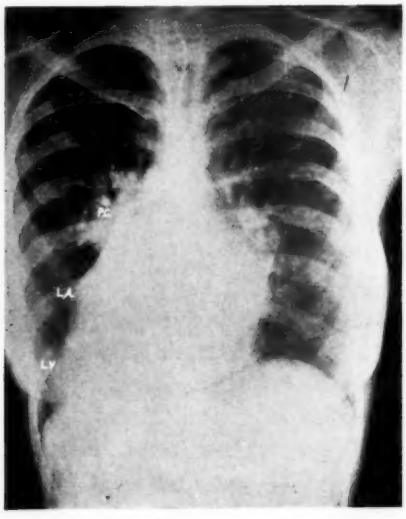

Fig. 1.

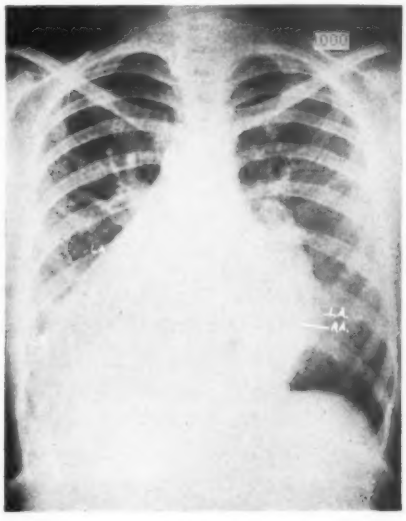

Fig. 2.

Fig. 1.—Case 3 showing the mitral shape of heart. L.V., left ventricle; L.A., left auricle; P.C., pulmonary curve.

Fig. 2.—Case 2 showing how the enlarged left auricle may project beyond the normal right border of the heart. Both auricles identified at fluoroscopy.

oblique, the left breast. In oblique and lateral rays of a normal chest there is no marked protrusion of any part of the back of the heart into the clear space of the posterior mediastinum.

The shape of the heart known roentgenologically as the mitral type is well recognized (Fig. 1). Vaquez and Bordet[32] deal very fully with this aspect of the subject in regard to the heart outline of this type in anteroposterior as well as in oblique views. The characteristic features from the front are an increase in the horizontal diameter, a widening above the ventricles, and the presence of an extra curve (L.A.) between the pulmonary cone shadow (P.C.) and the left ventricle (L.V.). In the lateral and in the right oblique positions the posterior surface

of the dilated auricle is smoothly spherical and shows as a definite, backward bulge about two to three inches above the diaphragm. The differential diagnosis of these films is, however, not easy.

That the left auricle, if enlarged, shows clearly in the right oblique position and may show even in the anteroposterior position as the upper portion of a double shadow on the right side (Fig. 2) is not so well recognized. The identity of this double shadow can be verified at fluoroscopy; a slight rotation to the right bringing the upper shadow into greater prominence, hence showing it to be posterior. A study of the pulsation may also help. In one of our cases, which was fibrillating, we found on fluoroscopic examination that these two curves pulsated asynchronously. During ventricular systole the left auricle

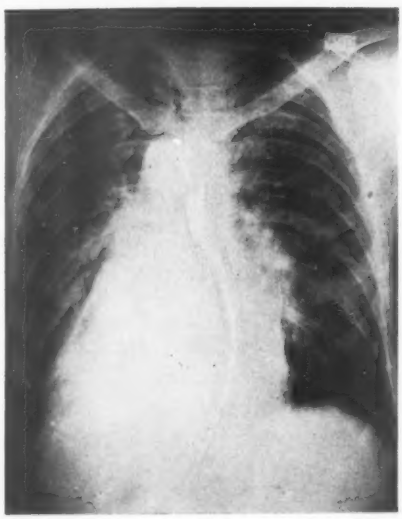

Fig. 3.

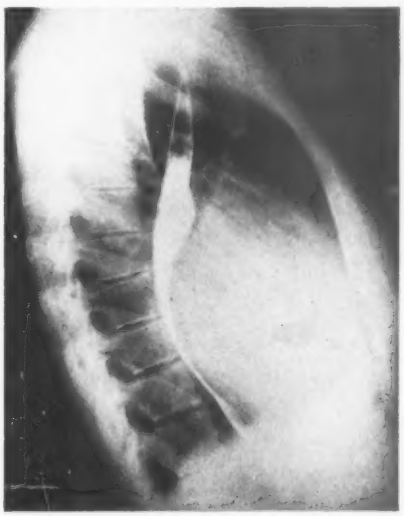

Fig. 4.

Fig. 3.—Case 1. Front view of chest while patient swallows barium emulsion, showing how the enlarged auricle displaces the esophagus to the right.

Fig. 4.—Case 3. Lateral view of chest while patient swallows barium emulsion, showing backward displacement and compression of the esophagus.

was ballooned out under pressure from the left ventricle through the incompetent mitral valve, while the right auricle, protected from pressure by the competent tricuspid valve, did not balloon out but rather seemed to contract.

Examination of the Esophagus.—

Examination of the esophagus in cases of mitral disease is not new but merits more common use in roentgenological examination. The patient is examined during the act of swallowing a thin barium suspension. Fluoroscopy is sufficient unless permanent records are desired. The normal esophagus passes directly down the mediastinum with a slight inclination to the right at about the middle of the thorax.

In the lateral views the indentations of the backs of the tracheal bifurcation, the aortic arch, and the left auricle on the anterior wall of the esophagus can be observed but are never prominent. An enlarged auricle presses the esophagus backward and, usually, to the right (Figs. 3 and 4), and on fluoroscopy the pulsation of the auricle, transmitted to the fluid barium in the esophagus, is strikingly shown. Since the displacement is to the right and backward, it should be seen at its maximum in the right oblique position (Fig. 5) and at the minimum in the left oblique position. In the latter position the esophagus should appear straight, as it is examined in the plane of the curve. This we found to be the case.

We have examined by this method a number of cases of heart disease other than mitral—including two enormous hearts, one in a case of hypertension and one in a case of congenital heart disease. In all of these the esophagus followed its normal course or was deviated to an extent which was relatively slight compared to the degree of general enlargement of the heart. In some cases of early mitral disease, too, the esophagus was normal in position, but in these, evidence of auricular enlargement was also lacking. One of us in examining a few cases of known mitral disease in young children found this same deviation of the esophagus in well-established cases. We have not observed any deviation to the left as was noted by Rösler and Weiss.[21]

Examination of the Trachea and Main Bronchi.—

The fact that enlargement of the left auricle may cause displacement and distortion of the bronchi has long since been shown on the autopsy table. It has only recently been demonstrated by x-ray. This was done by Gabert[31] in 1924 in anteroposterior views in which the main bronchi showed dimly but plainly enough to estimate the angle between them. By the use of the left anterior oblique position in addition to the anteroposterior view we find that we can visualize the bronchi more clearly and more frequently. By raying more densely and by the use of lipiodal in stout subjects, we can nearly always outline the course of the trachea and main bronchi. It is essential that films be made, for visualization of the bronchi under the fluoroscope is unusual unless lipiodol is used.

In anteroposterior films of the chest, the normal position of the bifurcation of the bronchus lies just to the right of the lower edge of the rounded shadow of the aortic arch in the left upper mediastinum. The angle between the right and left bronchi varies from 40 degrees to 70 degrees (apparently depending to some extent upon the build of the patient), as measured in a series of 6 foot anteroposterior films of normal chests after lipiodol injection. The average angle in twenty normal cases was 58 degrees with a maximum of 70 degrees and a minimum of 38 degrees. Allowing for the fact that the apparent angle in the film may be rather less than the real angle, these results

agree quite well with those of Stoerk.[3] In the left oblique position, which we found most useful in demonstrating bronchial abnormality, the angle is some five to ten degrees less than that of the corresponding anteroposterior films. In this same view, normal individuals usually show a certain amount of space between the shadows of the back of

TABLE I

VALUES OF THE TRACHEOBRONCHIAL ANGLES (FROM STOERK)

(A) NORMAL			
	RIGHT	LEFT	TOTAL
Average	24.38°	44.89°	69.27°
Extremes	19° to 35°	32° to 49°	58° to 78°
(B) IN MITRAL DISEASE			
	RIGHT	LEFT	TOTAL
Average	34.8°	60.3°	95.1°
Extremes	17° to 52°	51° to 73°	78° to 117°

the heart and left bronchus. Fig. 12 (A and B) shows tracings of the bronchi made from films taken after injection of lipiodol and illustrates the diminution of the bronchial angle in the change from the anteroposterior to the left oblique position. In stout subjects, especially, for anteroposterior views it may be necessary to inject a small amount of lipiodol to visualize the bronchi. In the left oblique view which was found more convenient and reliable for outlining the bronchi than any other, the procedure is seldom needed but is so simple and well established that its use seems justified in any case of cardiac enlargement in which there is doubt concerning the correctness of the diagnosis.

We have studied in considerable detail five cases of typical mitral disease and many of less certain clinical diagnosis. Observations were made also on several other types of heart lesions. That one may judge their value, summaries of these five clear-cut cases of mitral disease are included, as they have not yet come to autopsy. The illustrations are taken from these cases entirely except Figs. 10, 11, and 12 (A, B, C, D). The illustrations and the measurements of normal angles were made from films of individuals suspected of bronchiectasis in whom lipiodol was used and who showed no evidence of cardiovascular disease, or of pulmonary disease, sufficient in any way to admit of the possibility of bronchial distortion.

CASE SUMMARIES

CASE 1.—A white man, 47 years old, with symptoms of cardiac insufficiency for ten years and twice decompensated entered the medical service, after an acute febrile illness of five weeks, having developed a stabbing pain in the left chest the night before admission. Dyspnea and cough with a production of large amounts of purulent sputum were the chief complaints. He was dehydrated and dyspneic with a large heart, auricular fibrillation, a systolic blow and a low diastolic mur-

mur. The first sound at the apex was short and sharp, and the second pulmonic sound was much increased. The lungs were filled with moist râles, most numerous over the left base where there was dullness and a friction rub. The electrocardiogram showed auricular fibrillation and right ventricular predominance. Routine x-ray examination revealed an extra convexity of, and an increase in width of the left upper border. Further examination showed the esophagus displaced posteriorly to the right (Fig. 5) and a protrusion of the upper portion of the cardiac shadow posteriorly.

Improvement occurred slowly but after five weeks with the patient up and about on the ward, the râles and dullness at the left base posteriorly, persisted. The breath sounds varied, sometimes suppressed, and sometimes tubular in quality. The production of sputum continued at the rate of from two to four hundred c.c. per diem. Bronchiectasis was suspected, and an x-ray examination following lipiodol injection was done. There was no bronchiectasis, but the angle be-

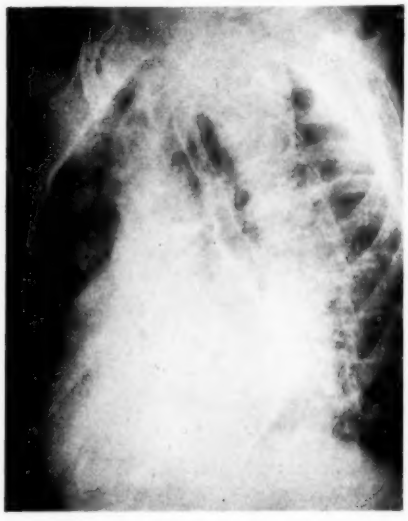

Fig. 5.

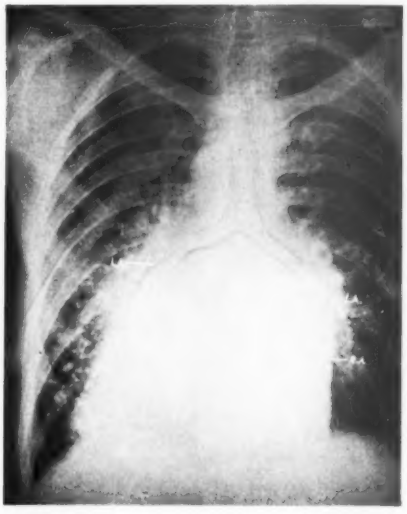

Fig. 6.

Fig. 5.—Case 1.—Right oblique view of chest while patient swallows barium, showing the esophageal displacement is most apparent in the right oblique position. A small diverticulum is present.

Fig. 6.—Case 1. Front view of chest after lipiodol injection of the bronchi showing distortion and compression of the left bronchus by the enlarged left auricle.

tween the bronchi was increased to approximately 90 degrees, and the left bronchus was turned upward and compressed at a point about 1½ cm. from the bifurcation of the trachea. The course could be made out in the anteroposterior film (Fig. 6) but was better seen in the left oblique position. In the latter, it could be followed even without the use of lipiodol (Fig. 7).

At the present time the physical signs at the left base persist as well as cough and production of moderate amounts of sputum, yet the patient is at home and now driving a taxicab nine months after his admission.

CASE 2.—A white woman, 24 years old, was admitted March 7, 1928, complaining of dyspnea and palpitation, first noted five years previously during the first pregnancy, recurring more severely during the second pregnancy one year later. Since then she has been free from symptoms, save on considerable exertion, until

two weeks before admission when a rapid increase in dypsnea occurred with the onset of almost continuous palpitation. On examination she was dyspneic, yet without any signs of congestive failure, the heart was quite large, 4 cm. to the left in the third interspace, 11 in the fifth, and just to the right of the sternum in the fourth. The apical rate was 140, and auricular fibrillation was proved by the electrocardiogram. Systolic and diastolic murmurs were definite, both best heard in the fourth left interspace. The x-ray and fluorscopic examinations revealed a heart greatly enlarged to the left and right, a biconvex right border, the two convexities of which pulsated asynchronously. There was a large backward bulge of the upper posterior border in the lateral view, which pulsated actively and on which the barium in the esophagus, which was displaced posteriorly and to the right, danced with the transmitted pulsation. The left oblique view showed a widening of the bronchial angle to 80 degrees and some compression and upward displacement of the left bronchus. A diagnosis of rheumatic endocarditis

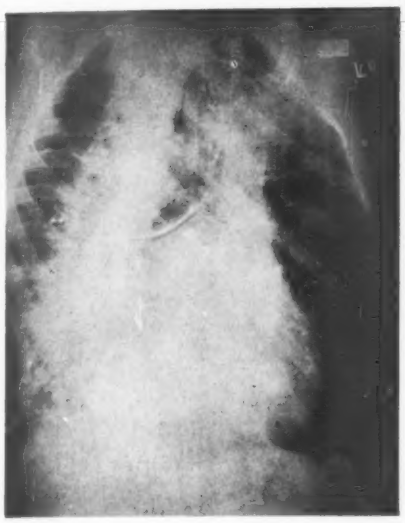

Fig. 7.

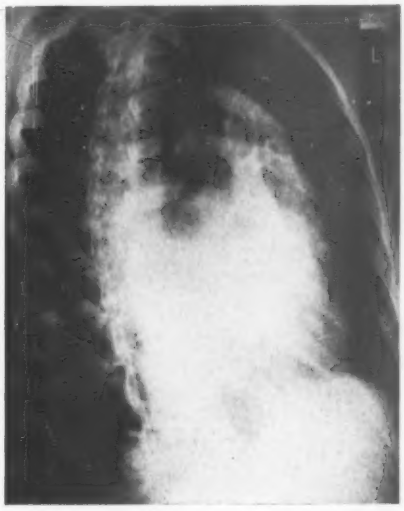

Fig. 8.

Fig. 7.—Case 1. Same as Fig. 6 in the left oblique position showing the compression and elevation of the bronchus very clearly.

Fig. 8.—Case 3. Left oblique view of the chest showing how distortion of the left bronchus can be seen in this position without previous lipiodol injection; contrast with Fig. 9.

with double mitral disease, insufficiency of the valve being more prominent, was made. The rate was easily controlled with digitalis, rapid improvement followed, and the patient is quite well doing housework at home.

CASE 3.—A white girl, 26 years old, entered the hospital on Feb. 28, 1928, with the complaint of heart trouble The history suggested acute rheumatic fever at eleven years of age, and she had been sent to a sanatorium three years prior to admission, for pulmonary tuberculosis. Cardiac symptoms had been present only one year, beginning with dyspnea, then attacks of nocturnal orthopnea, and for a few months edema of her ankles. The patient had been in bed for some months and on admission at rest showed no signs of cardiac insufficiency except slight cyanosis of the lips, not visible in the finger tips. The heart was moderately enlarged, regular, slow; the apical impulse was forceful, and there was a systolic shock. A loud crescendo presystolic murmur, heard best in the third and fourth

left interspaces inside the midclavicular line, and a soft systolic blow at the apex, were present, together with a snapping first sound at the mitral area, and made the diagnosis of rheumatic endocarditis with mitral stenosis quite definite. There was no evidence of pulmonary tuberculosis on physical examination. The electrocardiogram showed a notched P-wave in Leads I and II and a right ventricular predominance. X-ray examination revealed a moderately enlarged heart with a mitral configuration (Fig. 1). The lungs were clear. The esophagus was displaced backward (Fig. 4) and to the right. The left main bronchus was elevated (Fig. 8), making a total bronchial angle of 70 degrees, and bent upward about 3 cm. from the bifurcation. These findings served to confirm the clinical diagnosis.

The patient improved and six months later is still returning to the dispensary in about the same condition. Her physical activity is very limited, the cyanosis remains unchanged, but as yet no signs of congestive heart failure have made their appearance.

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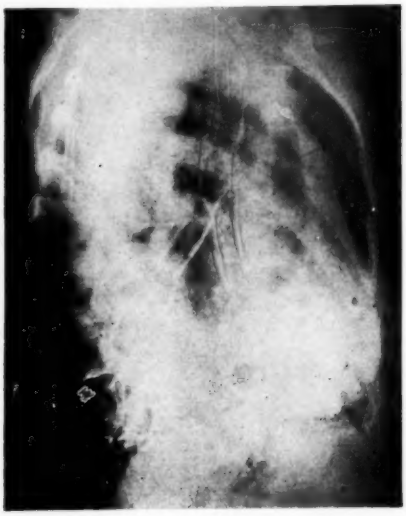

Fig. 9.

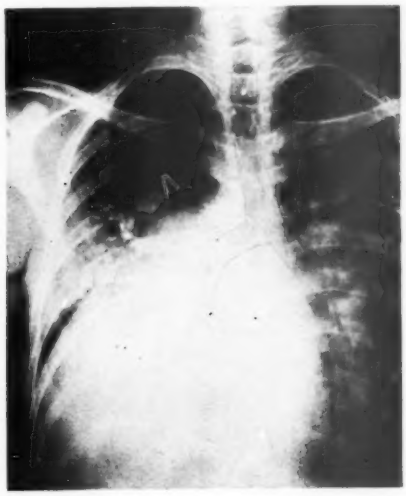

Fig. 10.

Fig. 9.—Left oblique view of the chest in a normal individual after lipiodol injection showing the normal bronchial angle in this position and the normal course of the left bronchus in contrast to Figs. 7 and 8.

Fig. 10.—Front view of the chest showing position of bronchi in a case with enlarged heart not due to mitral disease (case of patent ductus arteriosus) showing widening of bronchial angle but no distortion of the bronchus.

CASE 4.—A salesman, 43 years old, was seen in our out-patient department on Dec. 23, 1927, and subsequently admitted to the hospital, for study rather than therapy. His complaint was "shortness of breath and substernal pain." A definite history of acute rheumatic fever at the age of 31 and again at 36 years was obtained. Symptoms of dyspnea, palpitation, choking and dull precordial pain, usually only on effort, had been present for four years without much increase until one month before admission when a constant cough developed. On examination the patient presented an unusually slow pulse rate, 48 to 56, irregular, and unaffected by atropine. The heart was much enlarged, 13 cm. to left in the fifth interspace, and a systolic murmur and a long diastolic murmur were heard. The first sound was short and snappy at the apex. The electrocardiographic record was that of auricular fibrillation with a very slow ventricular rate occasionally with thirty or forty second intervals. The configuration of the heart in the x-ray film

was typical of the enlarged left auricle, the esophagus was displaced posteriorly and to the right. There was some widening of the bronchial angle to the upper limit of normal, namely 70 degrees. The upturning of the left bronchus 2 cm. from the bifurcation was well marked in the left oblique view. A diagnosis of rheumatic endocarditis with mitral stenosis was made.

The patient continues to return to the cardiac clinic, his clinical condition unchanged save that in spite of the low ventricular rate, the dyspnea and precordial pain seem slightly alleviated by digitalization.

CASE 5.—A salesman, 32 years old, came to our clinic first on Feb. 9, 1928. He had an indefinite history of acute rheumatism at the age of 14 years, and a typical attack of acute rheumatic fever at 26 years. Tonsillectomy was performed at 12 years of age because of frequent tonsillitis. Since the second attack of rheumatic fever six years before, dyspnea and dull precordial pain after exertion have been constantly present. Two years before examination he had several very small

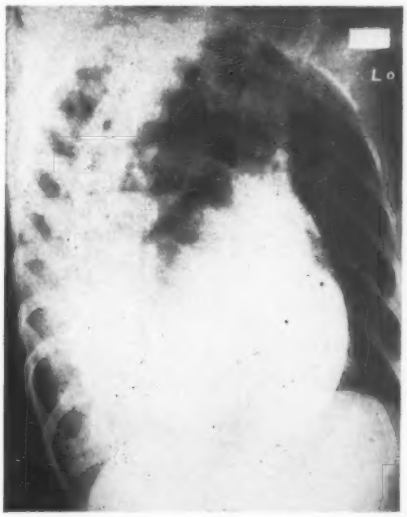

Fig. 11.—Left oblique view of the chest in a case of enlargement of the heart due to hypertension showing widening of the bronchial angle but no distortion.

hemoptyses and recently sudden attacks of dyspnea. The general examination was altogether negative. The heart was slightly enlarged to percussion, especially the upper left border, 5 cm. to left in third interspace, and a systolic murmur and crescendo presystolic murmur with a palpable thrill were present. Predominance of the right ventricle and notched auricular waves (Leads I and II) were noted in the electrocardiogram. The anteroposterior x-ray of the chest showed a well-marked curve between the pulmonary cone and left ventricular shadows. The lateral and left oblique views showed a posterior bulge of the cardiac shadow near the base, leaving the lower portion of the retrocardiac space clear. In the left oblique view the main bronchi were visualized and the angle between them measured 70 degrees while the left main bronchus showed a well-marked upward deflection 3 cm. from its origin in the trachea. The diagnosis of rheumatic endocarditis with mitral stenosis was made. His condition at present is unchanged. He is still carrying on his business and was advised to take a few hours additional rest.

Wassermanns on all these patients were negative. Unmentioned routine laboratory tests were either of little importance in the present connection or negative.

COMMENT

With regard to the outline of the enlarged left auricle, the appearance of the curve L.A (Fig. 1) is now generally recognized as pertaining to this organ, but we should like to emphasize the fact that the

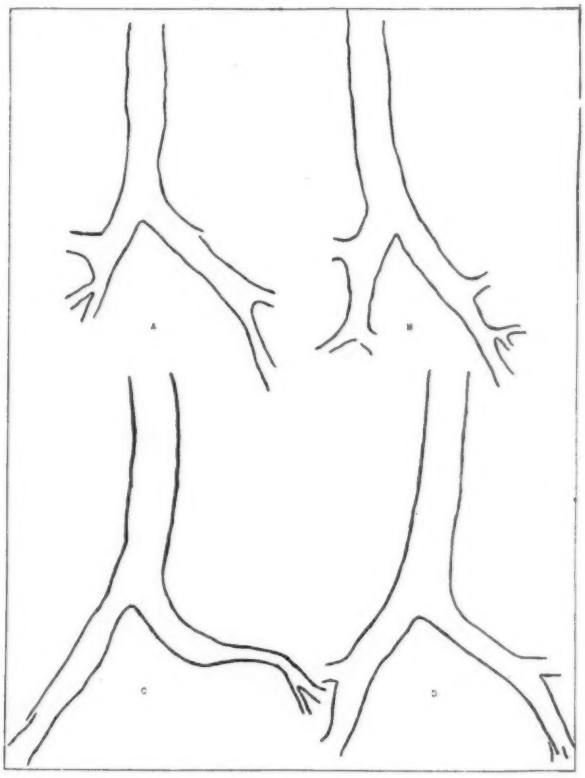

Fig. 12.—Tracing of trachea and bronchi made from films taken after lipiodol injection. (A) Normal case with average bronchial angle as seen in front view. (B) Same case, as seen in left oblique position. (C) Typical instance of elevation and compression resulting from enlargement of the auricle. (D) Widening of the bronchial angle without distortion associated with enlarged heart not due to mitral disease.

left auricle may appear as part of the upper right border of the heart in x-ray films long before it is detectable in physical examination. (Cases 1 and 2.) Fluoroscopy is here essential for two reasons. First, gradual rotation of the patient to the left ascertains that this upper convexity of the right border is identical with the posterior bulge of the heart. This in turn is generally agreed to be left auricle. Second, the occasional helpful finding of asynchronous pulsations of the two convexities, as noted in Case 2, may be present.

The deviation of the esophagus in mitral disease is well known but is not sufficiently used as a routine test. In passing, it may be noted that it has always been to the right and backward in our experience, as most observers have recorded. It does not usually occur to any noteworthy extent, even in cases of enormous cardiac enlargement unless the left auricle is involved in the enlargement.

Distortion of the left bronchus as a useful indication of left auricular enlargement is practically unknown. The result of the x-ray examination after lipiodol injection in Case 1 was rather a surprise, although the possibility of compression of the left bronchus as a cause of the lung findings in the left base had been suggested. The markedly widened bronchial angle of 90 degrees, the compression and especially the upturning of the left main bronchus (Figs. 6 and 7) precipitated this study. At that time we were unaware of Gabert's work. Then, when the left oblique views were found to show the bronchi still more clearly, and when by raying more densely it was possible to demonstrate the outline of the bronchi with a certain degree of regularity, the possibilities of a useful diagnostic method appeared.

In no case of known mitral disease was the bronchial angle less than 70 degrees, which we have already seen to be the upper limit of normal; while in the most marked cases it was over 90 degrees. The same 5 to 10 degrees less in the oblique views was true here as in the normal cases. The reported angles ranged from 90 to 70 degrees.

The notable feature about this distortion was not so much the widening of the bronchial angle as the manner in which the bronchus curved gradually upward, instead of the normal straight or downward curvatures. (Fig. 8.) The obvious elevation and distortion of the bronchus is easily observed as contrasted with the normal (Fig. 9). The same contrast is noticeable in the diagram in Fig. 12 (C) which illustrates the type of displacement and the manner in which the bronchus may be compressed.

We have examined also, several cases of cardiac enlargement due to causes other than mitral disease and have found that a moderate widening of the bronchial angle may occur, but to a much less extent for a heart with the same degree of enlargement. Neither have we ever observed in cases of heart disease other than those associated with auricular enlargement, the characteristic upturning and compression of the bronchus (Figs. 11 and 12 [D]).

An excellent illustration of this difference is to be found in Fig. 10 (compare with Fig. 6). This was a case of enormous cardiac enlargement in a Filipino man of 25 years, who had had symptoms of heart disease for three or four years, and in whom a definite diagnosis could not be made between a congenital heart lesion and rheumatic valvular disease. For two reasons it seemed certain that the left auricle did not participate to any great extent in the enlargement. First, there was no pro-

trusion of the posterior portion of the heart into the retrocardiac space. Second, we were able to demonstrate by lipiodol injection that the bronchi pursued a normal course save for a possible slight widening of the bronchial angle to 75 degrees, only 5 degrees above the upper limit of our normal series. This was the only change in spite of the fact that the enormous heart shadow bulged well to the left of the left bronchus (Fig. 10). Were the upper left shadow left auricle, the bronchus would be bent upward, compressed and would tend to ride the shadow.

At autopsy some pulmonary sclerosis and a very large patency of the foramen ovale (3 cm. in diameter) was all that could be found to explain the enlargement. The heart weighed 900 grams and the enlargement was mainly right sided, the right auricle, right ventricle and pulmonary cone and artery being enormous. The left auricle was little, if any, enlarged. This readily explains why the left bronchus was relatively undisturbed, since the pulmonary cone and artery are free to enlarge to the left anterior to the left bronchus, not bound under it as is the left auricle.

The only other conditions in which we have observed a distortion of the left bronchus similar to that found in enlargement of the left auricle are tuberculosis and tumor of the lungs. Extreme fibrosis or contraction of the left upper lobe may result in widening of the angle of deviation of the left bronchus, and even in the characteristic upturning noted in enlargement of the left auricle; but the obviousness of a pulmonary lesion sufficiently large to give this result precludes any confusion.

SUMMARY

The left auricle has a peculiar anatomical position, in that it is the posterior and superior chamber of the heart, thereby being in closest relation to the esophagus and to the bifurcation of the trachea. By virtue of this position the left auricle may enlarge to the right as well as to the left and during the course of its enlargement may exert pressure on the esophagus and main bronchi. There are many reports in the literature illustrating these effects, the least known of which is the last. Compression and displacement of the bronchi but rarely give rise to lung changes, yet may be frequently found by x-ray, and together with displacement of the esophagus are usually attributable to the left auricular enlargement.

Roentgenological methods demonstrating the occurrence of these three phenomena are described which make more accurate the diagnosis of enlargement of the left auricle.

1. Observation of right border of the heart for double curve in anteroposterior films and fluoroscopy to verify that the upper curve is identical with the posterior superior curve of the heart, and to note

asynchronous pulsations of the two curves. This last makes the diagnosis of left auricular enlargement quite definite.

2. Observation of displacement of the esophagus. The esophagus is displaced posteriorly and to the right by left auricular enlargement.

3. Demonstration of bronchial displacement, particularly as noted in the films made in the left oblique position—in obese patients, after an injection of lipiodol. Bronchial compression and displacement in left auricular enlargement occur frequently and can be demonstrated by x-ray study: (a) by left oblique views; (b) in anteroposterior views following lipiodol injection.

NOTE.—Since sending this article to the publishers the very excellent description of the position and outline of the left auricle has come to my notice: David Steel, "The Roentgenological Findings in Mitral Stenosis and Insufficiency," Amer. Jour. Roent. **21**: 221, March, 1929.

REFERENCES

1. Jaffe, H.: Die hokalization des linken Vorhofs des Herzens im Röntgenbilde, Zeitschr. f. klin. Med. **68**: 440, 1909.
2. Groedel, F. M., and T.: Über de Formen der Herzsilhouette bei der verschiedenen Klapperfehlen, Deutsche Arch. f. klin. med. **93**: 79, 1908.
3. Stoerk, O.: Beitrage zur Pathologie und Topographie des Mediastinum bei normaler und pathologischer Herzform, Ztschr. f. klin. Med. **69**: 32, 1910.
4. Owen, L., and Fenton, W. J.: A Case of Extreme Dilatation of the Left Auricle of the Heart, Clin. Soc. Tr. **34**: 183, 1901.
5. Emmanuel, J. G.: Extreme Dilatation of the Left Auricle, Lancet **1**: 591, 1923.
6. Shaw, H. B.: Horizontal Dilatation of the Left Auricle, Lancet **2**: 493, 1924.
7. Schott, A.: Zur Kenntnis der hochgradigen Erweiterung des linken Vorhofs, Klin. Wchnschr. **3**: 1057, 1924.
8. East, C. F. T.: Great Dilatation of the Left Auricle, Lancet **1**: 1194, 1926.
9. Lutembacher: Deux nouveaux cas d'Aneurysm de l'Oreilette, Arch. des mal. d. coeur **10**: 145, 1917.
10. Bedford, D. E.: Extreme Dilatation of the Left Auricle to the Right, AM. HEART J. **3**: 127, 1927.
11. Bramwell and Duguid: Aneurysmal Dilatation of the Left Auricle, Quart. J. Med. **21**: 187, 1928.
12. Neumann, W.: Die Bedeutung des Zweigeteilten rechten Vorhofbogens im Röntgenbilde, Deutsch. Arch. f. klin. Med. **137**: 129, 1921.
13. Assman, H.: Die Röntgendiagnostik der inneren Erkrankungen, Leipsig, 1921, Vogel.
14. Bordet, E.: Les Anomalies de developpement du profil de l'oriellette gauche dans le rétrècissement mitral, J. de Méd. **41**: 227, 1922.
15. Joachim, G.: Vier Falle von Storung der Reizleitung im Herzmuskel, Deutsche Arch. f. klin. Med. **80**: 373, 1905.
16. Minkowski, O.: Die Registrierung der Herzbewegungen am kinken Vorhof, Deutsche med. Wchnschr. **32**: 1248, 1906.
17. Eichorst, H. L.: Handbuch der speziellen Pathologie und Therapie, Berlin and Wien, 1905, Urban and Schwarzenberg **2**: 63, 1905.
18. Kovacz and Stoerk, O.: Ueber das Verhalten des Oesophagus bei Herzvergrösserung, Wien. klin. Wchnschr. **23**: 1471, 1910.
19. Von Faulkenhausen, M. F.: Oesophagus Kompression an zwei Stellen bei arteriosclerotischer Herzinsufficienz, Deutsch. med. Wchnschr. **47**: 743, 1921.
20. Gabert, E.: Die Lagebziekung des Oesophagus zur dorsalen Herzflache und ihre Veranderung durch Erweiterung des linken Vorhofs in Roentgenbilde, Fortschr. a. d. Geb. f. Rontgenstrahlen **32**: 410, 1924.
21. Rösler, H., and Weiss, K.: Über die Veränderung des Oesophagusverlaufes durch den vergrosserten linken Vorhof. Fortschr. a. d. Geb. d. Röntgenstrahlen **33**: 717, 1925.
22. Notkin, M.: Paralysis of Left Recurrent Laryngeal Nerve in Mitral Stenosis, Arch. Int. Med. **33**: 71, 1924.

23. Steele, J. M., Jr.: Compression and Displacement of the Bronchi in Mitral Stenosis, AM. HEART J. 4: 53, 1928.
24. King, J. W.: On a Morbid Flattening and Compression of the Left Bronchus by a Dilatation of the Left Auricle, Guy's Hosp. Rep. 3: 175, 1838.
25. Friedreich, N.: Virch. Spec. Path. and Therap. vol. v, Part 2, p. 230, Berlin, 1867, Ferdinand Enke.
26. Taylor, H. H.: Tr. Path. Soc. (London), 40: 58, 1889.
27. West, Samuel: Diseases of the Organs of Respiration, London, 1909, C. Griffin & Co. 1: 108; Sansom, A. E., and Gibson: Diseases of the Mitral Valve, Allbutt and Rolleston's System of Medicine 3: 343, 1909, Philadelphia and London, W. B. Saunders Co.
28. Aeby, C. T.: Der Bronchialbaum der Saügetiere und des Menschen, Leipzig, 1880, Engelman.
29. Von Hovorka and Kobler: Referred to by Stoerk. See Ref. 3.
30. Kahler: Bronchostenose bei Vorhofvergrösserung, Monatschr. f. Ohrenh. 46: 573, 1912.
31. Gabert, E.: Der hintere Herzrand im Röntgenbild in normalen und kranken Fallen und Veränderungen des Tracheo-bronchial baumes durch Erweiterung des linken Vorhofs, Fortsch. a. d. Geb. f. Röntgenstrahlen 32: 385, 1924.
32. Vaquez and Bordet: The Heart and the Aorta. New Haven, 1920, Yale University Press.

TRANSITORY VENTRICULAR FIBRILLATION AS A CAUSE OF SYNCOPE AND ITS PREVENTION BY QUINIDINE SULPHATE*

With Case Report and Discussion of Diagnostic Criteria for Ventricular Fibrillation

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THE diagnosis of ventricular fibrillation cannot be proposed for electrocardiograms of patients with the assurance usual in classifying records of arrhythmias. The experimental evidence on which the interpretation of the curves must be based has not been so thorough or convincing that one may state whether any questionable record should be classified as ventricular tachycardia, flutter or fibrillation. With these facts in mind I wish to present a patient with syncopal attacks as the presenting complaint, in whom during such an attack, induced by injecting epinephrine, ventricular arrhythmia of bizarre type was recorded.

CASE REPORT

Mr. E. S., married and father of several normal children, had been subject to dyspnea and fatigue on exertion "all his life." Between the ages of 28 and 33 years he had numerous attacks of arthritis of knees and ankles, with little or no fever.

He was 36 years old when he had his first syncopal attack, which occurred while he was at rest. Three weeks later he had a similar attack, and these attacks occurred at intervals of about one month from April, 1926, until April, 1927. They then became more frequent and variable in severity up to October 15, 1927. Between October 15 and 25 they occurred one or more times daily. He had always considered himself a nervous man, and this irritability was increased at this time. The noise made by his children often was the precipitating factor for the attacks.

He described his attacks as follows: A sudden sensation of heaviness in the chest seized him, and seemed to well up toward his head. The skin felt as though warm water were rising over it. When the sensation reached the chin level, he became weak and had to hold on to something to keep from falling. When it reached the level of his nose, he lost all muscular control, became blind and fell to the floor. He thought he had only lost consciousness once, and then for two minutes. Usually the attacks stopped before he became blind, and after the attacks passed off he was weak and tremulous for from twenty to thirty minutes. During the attacks his physician noted that pulse and heart sounds were absent.

On October 26, while in the office of Dr. R. B. McKenzie, he had a mild attack, the termination of which was recorded electrocardiographically (Fig. 1). He then entered the hospital and during five days of bed rest had no attacks.

He was a well-developed man, somewhat over-alert but not sick. There was marked dental caries with pyorrhea. The heart and lungs were quite normal, blood pressure

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was 140 mm. systolic, 85 mm. diastolic. The blood, urine, Wassermann and teleroentgenogram of the heart were all normal. The electrocardiogram was normal except for rare ventricular extrasystoles, all arising in the same region.

The patient was given epinephrine 0.2 c.c. of 1/1000 solution intravenously. Marked nervousness, tremor and sinus tachycardia occurred; no extrasystoles were produced. Within ten minutes the effect had almost entirely subsided. Fifteen minutes after the first injection a second dose of 0.3 c.c. was given. Before the record (Fig. 2) was started or the needle was out of the vein, the attack came on, and this was quite typical of the attacks observed by his home physician several times in the previous two weeks, during which the patient was pulseless, no heart sounds were audible and weakness and blindness came on within half a minute. The whole attack lasted about one minute, but he was very weak for half an hour.

He was put on constant medication with quinidine sulphate 0.3 gm. three times a day and in the year following this had but one attack of syncope. This was

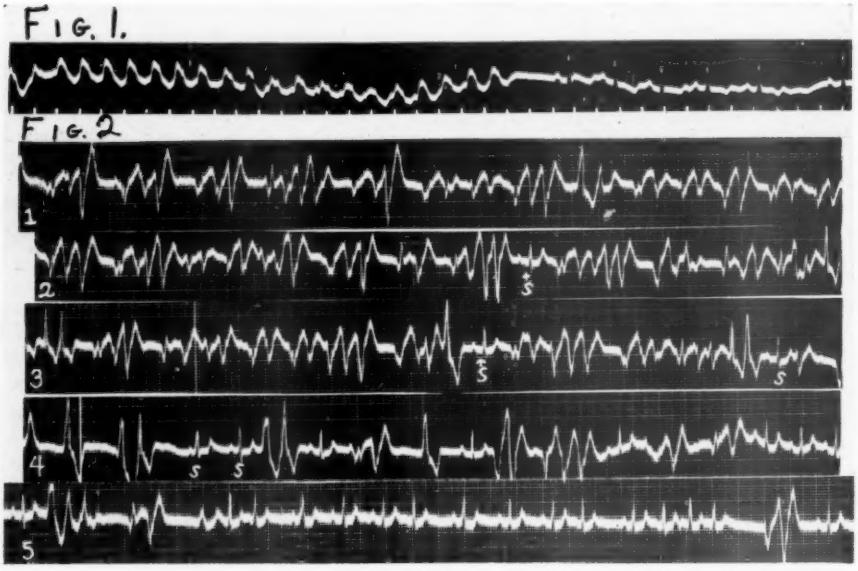

Fig. 1.—Termination of spontaneous attack of ventricular arrhythmia, rate 285 per minute. Time in 1/5 seconds.

Fig. 2.—Consecutive tracings during an attack induced by epinephrine. Two seconds of sinus rhythm omitted between Nos. 4 and 5. Note sinus beats (marked with *S*) interpolated without postundulatory pause in Nos. 2 and 3.

during the removal of his carious teeth under local anesthesia. He found that when he discontinued quinidine for a few days he was troubled by fleeting sensations of precordial heaviness, and this difficulty persisted even after his gums had been healed over for six months. His tendency to fatigue easily and to become short of breath on exertion was unchanged.

Summary.—A middle-aged man, who had always had symptoms suggestive of effort syndrome, had syncopal attacks with increasing frequency for eighteen months. After quinidine rationing the attacks no longer occurred. Electrocardiograms were obtained during one mild spontaneous and one severe attack induced by giving epinephrine.

DESCRIPTION OF ELECTROCARDIOGRAMS

The tracing (Fig. 1) obtained during a brief spontaneous attack shows a ventricular tachycardia (rate 280), with moderate variation in shape and duration of electrcial complexes. There is no iso-electric period. The normal rhythm begins after a short pause; it is at first rapid but soon returns to a rate of 58 per minute.

The tracing (Fig. 2) obtained during the attack induced with epinephrine is of an entirely different sort. The ventricular rate varies between 190 and 200 per minute, although toward the end of the attack much slower rates of deflection can be noted for 2 to 4 complexes. There is no dominant form of electrical complex but the widest variation in shape with a tendency to have a few more or less similar waves followed by groups wholly different. About thirty seconds after the beginning of the attack a single sinus beat of normal shape, and not preceded by a pause, is interpolated in the tachycardia. Similar beats occur more frequently, then in twos and threes, and finally the attack terminates in a run of rapid sinus beats with occasional brief runs of abnormal ventricular complexes.

DISCUSSION

The cardiac activity represented by the oscillations recorded in Fig. 2 is obviously of quite a different order from the usual ventricular tachycardia, and it may be doubted that this attack induced with epinephrine is the same as the patient's spontaneous attacks. Subjectively the attack was quite like his severe seizures, and we know that in other cases where similar doses of the drug have been given to patients with a tendency to ventricular arrhythmia the effect was to produce attacks which were quite similar to the spontaneous ones[1] or to cause merely a sinus tachycardia.[2] In this patient a dose only one-third smaller had evoked no ectopic rhythm.

To classify these tracings it is necessary to review those ventricular arrythmias which lie beyond simple tachycardia. In the German literature[3] the same scheme is used as with the auricular arrhythmias, and they designate as flutter those with continuous dentate oscillations of fairly regular form, and as fibrillation those with irregular and rounded oscillations. English and French authors avoid the term "ventricular flutter" and substitute "pseudofibrillation," "phase ondulatoire" or "those preliminary disturbances which precede" fibrillation.[4] These observers attach prognostic rather than physiological significance to these distinctions, for as MacWilliam[5] states of the conditions in the exposed heart of experimental animals, "from the evidence afforded by inspection, palpation, tracings of the oscillations, fall of blood pressure, etc., the two conditions (fibrillation and pseudofibrillation) may be impossible of distinction, but they differ strikingly as regards persistence; pseudofibrillation ceases immediately or at vary-

ing short periods after the cessation of the stimulation, while true fibrillation under ordinary circumstances goes on as a rule to the death of the heart.'' This distinction between fibrillation and the stage which precedes it, based wholly on prognosis, is of no value in human physiology, for the tendency of fibrillation even when fully developed in man is toward early spontaneous arrest of the arrhythmia. No one would accept a division of auricular fibrillation into pseudo and true on a basis of persistence, although here the difference in duration of paroxysmal and permanent attacks is a question of years. It is obvious that such a distinction is even more absurd for ventricular fibrillation where persistence for eight or ten minutes means death. With regard to the distinction between flutter and fibrillation, it is well to recall that in auricular flutter it is possible to demonstrate A-V conduction, usually with partial block, as well as motion of the auricles and of blood in the great veins due to the fact that the auricular muscle still contracts as a unit. Similar motion of ventricular muscle has never been demonstrated in the so-called ventricular flutter in man. Lewis[4] has shown that in the early stage of ventricular fibrillation in the dog the oscillations are quite similar in regularity and shape to the dentate oscillations of auricular flutter; yet at this time the carotid pressure scarcely fluctuates from zero, and the ventricular myocardiogram is a straight line. It seems certain that we will have to content ourselves with the diagnosis of tachycardia for those cases where persistent heart sounds or other pulsatile activity of ventricles is present, and fibrillation for those where gross mechanical arrest is present with persistent electrical oscillations. The more rapid and irregular these oscillations, the more certain can we be of advanced disturbance in the conduction of the circus movement, but slower and more regular oscillations are compatible with a dilated and fibrillating ventricle as may easily be observed with the exposed dog heart.

With these facts in mind it seems quite proper to suggest that both attacks recorded in this patient were due to ventricular fibrillation, the spontaneous one having a more rapid and regular oscillation than the induced attack. The conditions under which the latter occurred, the slower rate and great number of brief pauses suggest that the condition resulted from the depressant action of epinephrine, rather than from its sympathecticomimetic action.

This brings us to a consideration of the factors which produce or initiate ventricular fibrillation.[6] Experimentally fibrillation can be produced by faradization, and even in some species by a properly timed single shock to the ventricle or by massage or heating, by ligation or injection of emboli into the coronaries, or by alterations in vagal and sympathetic tone. A wide variety of drugs produces this arrhythmia: potassium, barium, pilocarpine, quinidine, digitalis, nicotine, cocaine, chloroform and epinephrine. The latter is unique in that small doses

may cause and large ones arrest ventricular fibrillation. Clinically the following facts seem well established: electric shocks, chloroform anesthesia and disease of coronary arteries may cause ventricular fibrillation and death. The great majority of clinically recorded cases of ventricular fibrillation occurred in patients with permanent A-V block shortly before death from myocardial disease or at the time of death in patients with other diseases. It has been assumed that sudden death occurring after emotional shocks, or in patients with angina pectoris, aortic insufficiency and the like are due to ventricular fibrillation, and deaths from digitalis and from quinidine are attributed to a similar mechanism. In patients with advanced myocardial disease the tendency to ventricular arrhythmia, especially under digitalis, is marked and may terminate in fibrillation.

We noted previously that of the score of cases of ventricular fibrillation recorded electrocardiographically, only one in a patient dying of heart disease, and two in cases in which the dying heart was recorded in patients with infectious disease were truly terminal, all the rest were transitory and this, in spite of the unfavorable conditions—complete heart-block, quinidine poisoning or moribund febrile state—which led to the occurrence of the arrhythmia. The most rapid ventricular fibrillation ever recorded in man terminated abruptly and the patient recovered,[7] while in thirty-seven moribund patients studied by various groups, only five showed transient fibrillation and two terminal fibrillation.[8, 9, 10, 11] I think that we must conclude from this that ventricular fibrillation is not easily established or maintained in man.

Nothing has been reported concerning treatment of attacks or prophylaxis in man. If we may judge from animal experiment, the intracardiac administration of full doses of epinephrine, or of potassium chloride, chloral hydrate or camphor would be worthy of trial in the attacks, and quinidine or digitalis as prophylaxis. We used quinidine in this case because of Scott's report[1] of its effectiveness in ventricular tachycardia, and the result seems to have been excellent.

SUMMARY

The significance and diagnosis of ventricular fibrillation is discussed with reference to a patient without evidence of organic heart disease, who had for eighteen months attacks of syncope due to transitory ventricular fibrillation. Quinidine sulphate rationing prevented these attacks.

REFERENCES

1. Scott, R. W.: Observations on a Case of Ventricular Tachycardia With Retrograde Conduction, Heart **9**: 297, 1921.
2. Levine, S. A., and Matton, M.: Observations on a Case of Adams-Stokes Syndrome, Showing Ventricular Fibrillation and Asystole Lasting Five Minutes With Recovery Following the Intracardiac Injection of Adrenalin, Heart **12**: 271, 1926.

3. deBoer, S.: Kammerflattern und Kammerflimmern bei einem Patienten mit totalen Herzblock, Ztschr. f. d. ges. exp. Med. **38**: 191, 1923.
4. Lewis, T.: The Mechanism and Graphic Registration of the Heart Beat, London, 1924, Shaw and Sons, p. 363.
5. MacWilliam, J. A.: The Mechanism and Control of Fibrillation in the Mammalian Heart, Proc. Roy. Soc. **90**: 302, 1918.
6. Gallavardin, L.: La fibrillation ventriculaire, J. de méd. de Lyon, **8**: 453, 1927.
7. Kerr, W. J., and Bender, W. L.: Paroxysmal Ventricular Fibrillation With Cardiac Recovery in a Case of Auricular Fibrillation and Complete Heart Block While Under Quinidine Sulphate Therapy, Heart **9**: 269, 1921.
8. Robinson, G. C.: A Study With the Electrocardiograph of the Mode of Death of the Human Heart, J. Exper. Med. **16**: 291, 1912.
9. Dieuaide, F. R., and Davidson, E. C.: Terminal Cardiac Arrythmias, Arch. Int. Med. **28**: 663, 1921.
10. Schellong, F.: Electrocardiographische Beobachtungen am sterbenden Menschen, Arch. d. ges. exper. Med. **36**: 297, 1923.
11. Kahn, M. H., and Goldstein, I.: The Dying Human Heart, Am. J. M. Sc. **168**: 388, 1924.

ELECTROCARDIOGRAPHIC CHANGES IN DIPHTHERIA

II. Intraventricular Block*

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ONE of the most striking clinical features in some cases of diphtheria is the extreme toxicity of the patient with a condition of the circulatory system bordering on collapse. Low blood pressure and feeble peripheral pulses, poor heart sounds and gallop rhythm are indications of cardiac dilatation, which is demonstrable clinically and has been observed roentgenologically. Such signs may be associated with slow or rapid heart rates and with irregular rhythms suggesting heart-block or independent ventricular tachycardias, which give serious prognosis. Electrocardiographic studies often reveal only a normal cardiac mechanism with intraventricular block varying from merely delayed QRS interval to typical bundle-branch block.

It is the purpose of this paper to call further attention to these phenomena and to consider the progress of these abnormalities from rather mild effects to more severe ones and to death in some cases, or to complete clinical and electrocardiographic recovery in others. Six cases were studied. Many other instances of delayed intraventricular conduction were observed, but they were accompanied by complete heart-block and have been considered in a previous article.[1] This paper suggests that the intraventricular block is frequently the result of a functional depression of the conduction system, rather than an anatomical change.

A brief summary of the cases and a description of the records follow. Measurements were made by projecting electrocardiographic films on a screen so that time intervals of 0.04 second equalled 0.5 inch. Readings were taken with a ruler.

CASE REPORTS

Case 1.—A negro boy, 5 years old, received 40,000 units of antitoxin on admission to the hospital. As no clinical history was ever obtained, the previous duration of illness remained unknown. The patient was very sick with low blood pressure and a pulse rate of 120 for six days, followed by marked improvement. On the twenty-seventh day in the hospital, nystagmus and petechiae of the skin appeared, and lumbar puncture showed 152 mononuclear cells and globulin. A diagnosis of tuberculous meningitis was made. Death occurred the next day after clonic convulsions.

An electrocardiogram on the ninth day in the hospital shows normal mechanism with regular rate of 80. The P-R interval is about 0.18 second. Ventricular com-

*From the Department of Medicine, Western Reserve Medical School at Cleveland City Hospital.

plexes show splintering, they are diphasic in Leads I and II, and inverted in Lead III. The QRS interval varies from 0.13 to 0.14 second in Lead I. The T-wave is upright in all leads (Fig. 1). A record taken on the following day is similar, but the excursion is greater in Lead I (Fig. 2). The next record, taken on the eleventh day, is similar to the first two described except that the splintering of

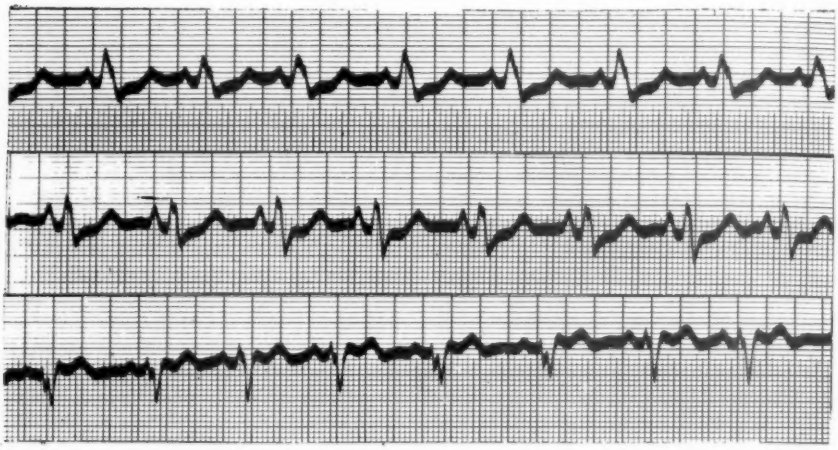

Fig. 1.—Case 1. Record on ninth day in the hospital. Normal mechanism. Marked splintering of ventricular complex with QRS interval of 0.14 second.

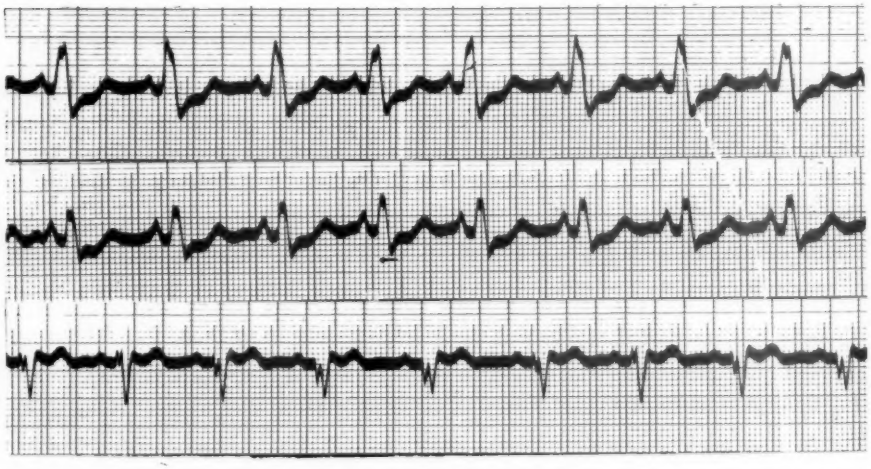

Fig. 2.—Case 1. Record on the following day, similar to the previous, but the excursions of Lead I are increased.

QRS has completely disappeared and the interval is reduced to from 0.10 to 0.12 second in all leads. Left ventricular preponderance is still marked (Fig. 3). The last record, taken on the fourteenth day, is normal. QRS interval is 0.08 second. Lead III is of low amplitude and T-waves are inverted here (Fig. 4).

Case 2.—A white girl, 6 years old, received 40,000 units of antitoxin after entering the hospital on the third day of the disease. She improved gradually and

was discharged after forty-five days in the hospital, with instructions to spend most of her time in bed for the next two weeks.

About the eighth day in the hospital her pulse fell to 60 where it remained until the twelfth day when it rose to about 100. An electrocardiogram taken on the eleventh day shows a rate of about 60 with a regular rhythm interrupted by auricular or nodal extrasystoles. This might be considered complete heart-block

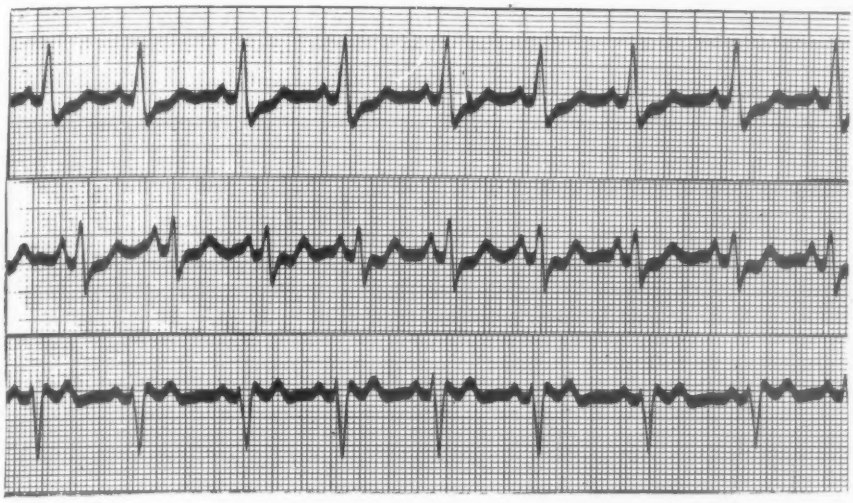

Fig. 3.—Case 1. Record on the eleventh day. Splintering of ventricular complexes has disappeared, and QRS interval is reduced to from 0.10 to 0.12 second.

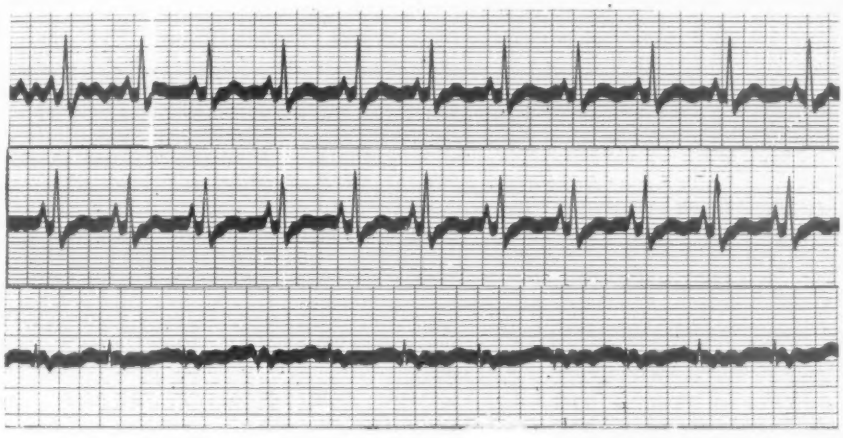

Fig. 4.—Case 1. Record on the fourteenth day is normal.

with independent ventricular rhythm, but the fifth complex of Lead I, the last complex of Lead II, and first, third, fifth and last complexes of Lead III definitely follow P-waves. Where ventricular action follows auricular contraction shortly after the preceding systole, the QRS complexes are smaller than usual but have the same general form as the others. QRS complexes in Leads II and III are diphasic and the interval varies from 0.14 to 0.16 second (Fig. 5).

A record taken three days later shows a normal mechanism except for auricular extrasystoles, the fourth complexes in Leads I and II. The P-R interval is normal, QRS complexes are upright and notched in all leads, and the interval is delayed to 0.12 second. The T-wave is constantly inverted (Fig. 6).

Five more records were made, all showing progressive improvement. The last record, made three days before discharge, shows a regular mechanism, normal P-R interval and normal QRS complexes except for low voltage. T-wave is inverted in Leads II and III (Fig. 7).

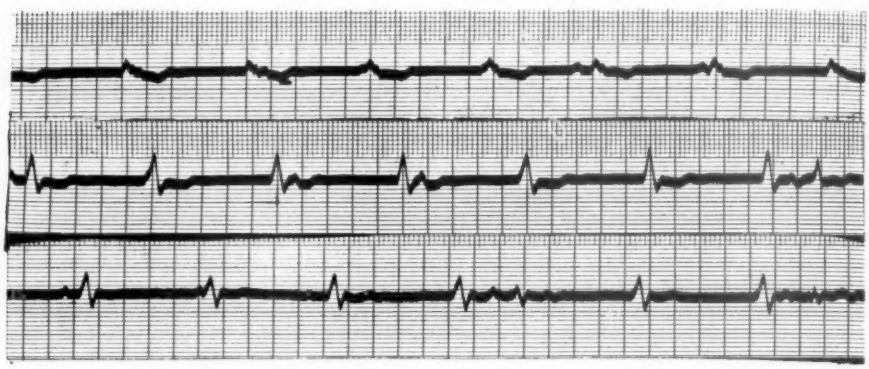

Fig. 5.—Case 2. Record on the eleventh day showing nodal rhythm with auricular extrasystoles. Marked widening of QRS complexes from 0.14 to 0.16 second.

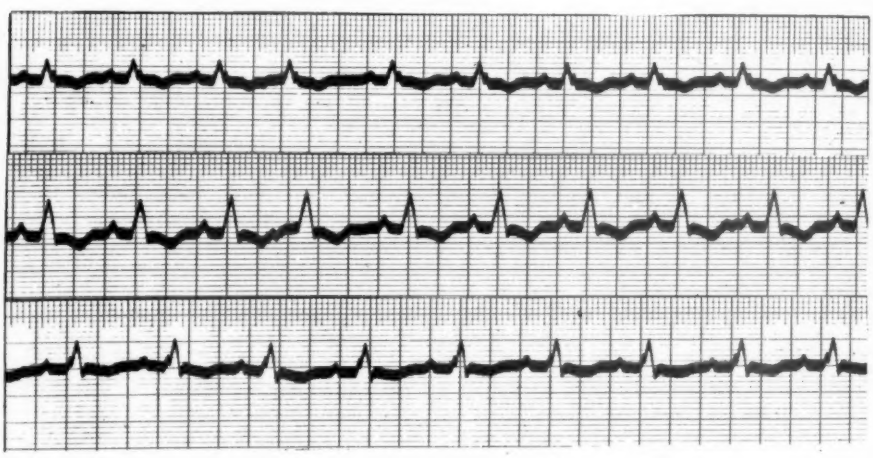

Fig. 6.—Case 2. Record on the fourteenth day shows splintering of venticular complexes with QRS interval of 0.12 second. The rhythm is regular except for isolated auricular extrasystoles in Leads I and II. T-wave is constantly inverted.

CASE 3.—A white girl, 13 years old, received some injections into the buttocks from the family doctor on the sixth day of the disease and entered the hospital on the eighth day, receiving 2,000 units of antitoxin at that time. She improved steadily during her stay and was discharged with pharyngeal paralysis after thirty days in the hospital.

An electrocardiogram taken on the fifth day in the hospital shows a regular rhythm and rate of 70. The P-R interval is fully 0.2 second. QRS complexes

are notched in all leads, upright in Leads I and II and inverted in Lead III, and measure from 0.14 to 0.15 second. The T-waves are opposite in direction to the main ventricular complexes in Leads I and III. This record shows right bundle-branch block, though the excursions are not so great as are usually seen (Fig. 8).

A record two weeks later shows a marked change toward normal (Fig. 9).

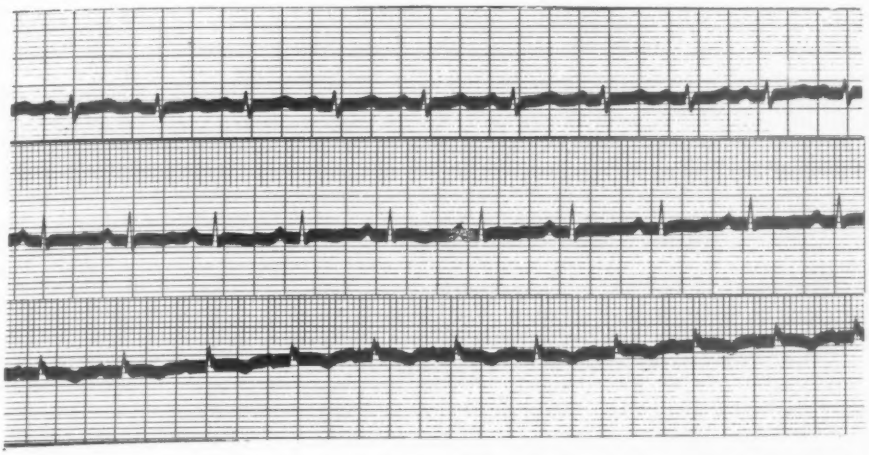

Fig. 7.—Case 2. Record before discharge from hospital. It is essentially normal except for low voltage and inverted T-waves in Leads II and III.

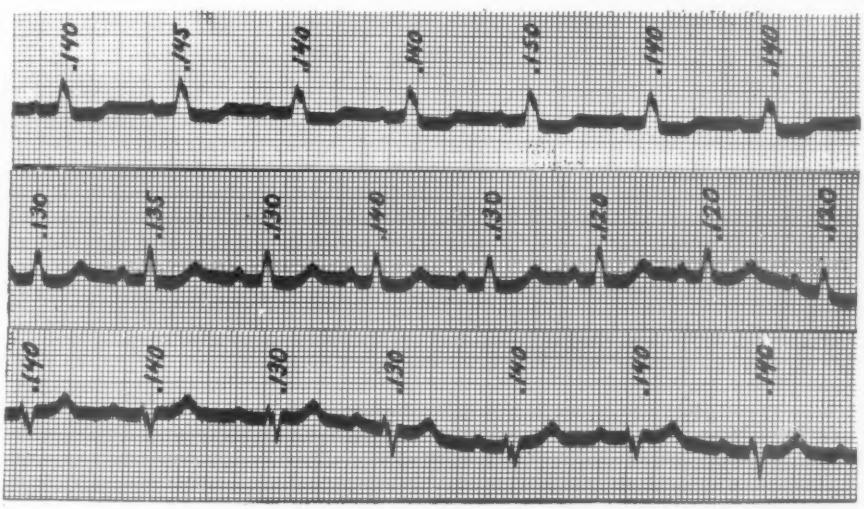

Fig. 8.—Case 3. Record on the fifth day showing splintering of ventricular complexes. QRS interval prolonged to 0.15 second and T-waves opposite in direction to that of main deflection. This record shows right bundle-branch block. P-R interval is 0.2 second.

Case 4.—A white boy, 7 years old, received 40,000 units of antitoxin on admission to the hospital the fourth day of the disease. He was very ill with a pulse rate of 140 and blood pressure of 85/45 mm. He developed gallop rhythm and cardiac dilatation on the third day in the hospital, which persisted until the

twenty-eighth day. Improvement was progressive, however, and he was released on the thirty-first day to the care of his family physician with the understanding that he would remain in bed for two weeks.

The first electrocardiogram taken on the third hospital day reveals a regular rhythm with a rate of 120. The QRS complexes are upright, notched in all leads and show an interval of from 0.10 to 0.12 second. The T-waves are upright in

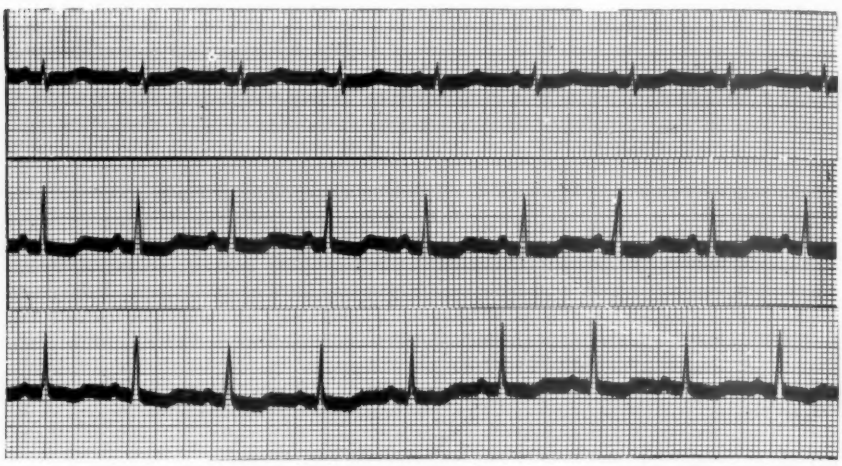

Fig. 9.—Case 3. Record taken two weeks later, which is essentially normal.

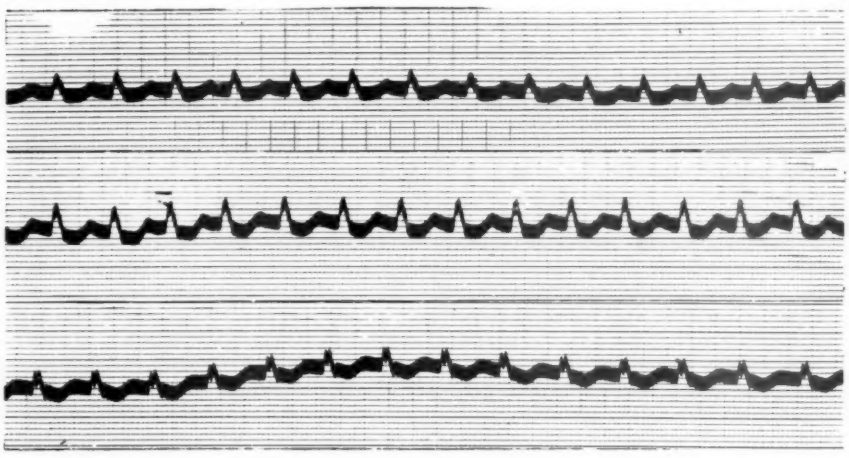

Fig. 10.—Case 4. Record on third day in the hospital shows ventricular complexes upright and splintered and QRS interval of from 0.10 to 0.12 second.

Leads I and II and inverted in Lead III. The voltage is low (Fig. 10). A record taken four days afterward shows notched QRS complexes with an interval of 0.12 second. These complexes are upright in Lead I and inverted in Leads II and III. The T-waves are opposite in direction to the initial ventricular complexes in all leads. The voltage is still low, otherwise the record suggests right bundle-branch block (Fig. 11). A record taken on the fifteenth hospital day shows notched

QRS complexes, but the interval has decreased to 0.08 to 0.10 second. They are upright in all leads but the voltage remains low (Fig. 12).

CASE 5.—A white girl, 7 years old, received 40,000 units of antitoxin on admission to the hospital on the fifth day of the disease. She was acutely ill; the blood pressure was low, and the pulse was feeble. There was no improvement in her condition, and on the fourteenth day she vomited, became cyanotic and pulseless, and died in a few hours.

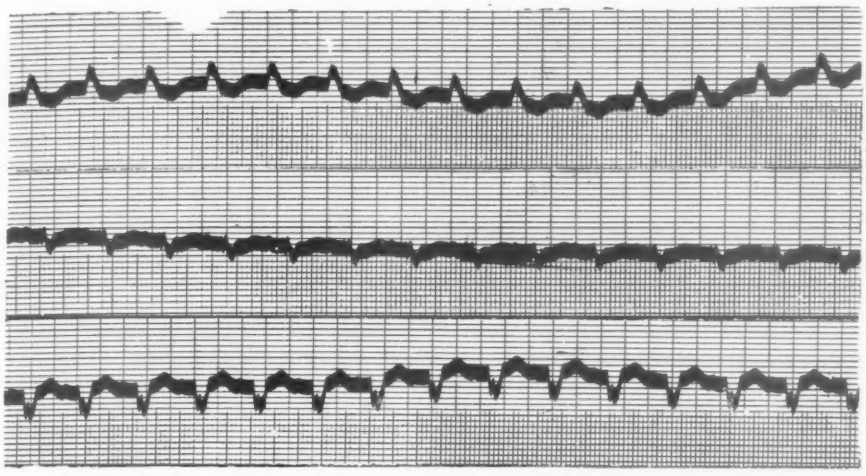

Fig. 11.—Case 4. Record four days later showing right bundle-branch block.

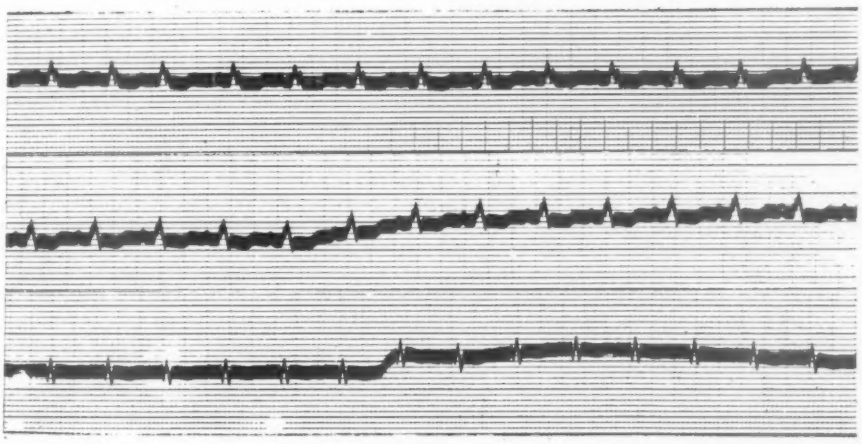

Fig. 12.—Case 4. Record on fifteenth hospital day showing definite change toward normal.

An electrocardiogram taken on the eleventh hospital day shows regular mechanism with a rate of 90. P-R interval is within normal limits. The QRS complexes are upright in Lead I and inverted in Leads II and III. The QRS complexes in Leads II and III are splintered, and the QRS interval is 0.14 second. The T-waves are opposite in direction to the initial ventricular complexes in all leads (Fig. 13). This record shows right bundle-branch block.

CASE 6.—A white girl, 10 years old, received 40,000 units of antitoxin on admission to the hospital on the seventh day of the disease. She experienced some difficulty in swallowing for several days due to swelling of the neck. The systolic blood pressure was consistently about 80 mm. and the diastolic varied from 0 to 40 mm. She seemed to be improving gradually, however, until the eighth day in the hospital when she suddenly collapsed and died.

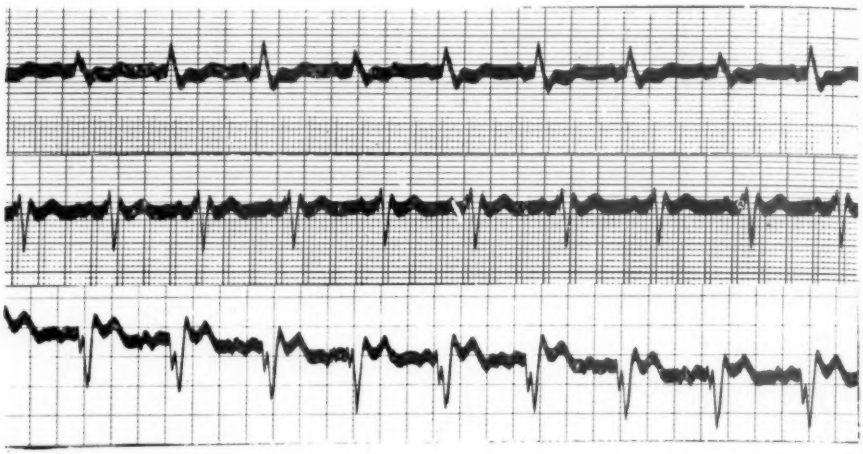

Fig. 13.—Case 5. Record taken three days before death, showing splintering of ventricular complexes and delayed QRS interval of 0.14 second. This record shows right bundle-branch block.

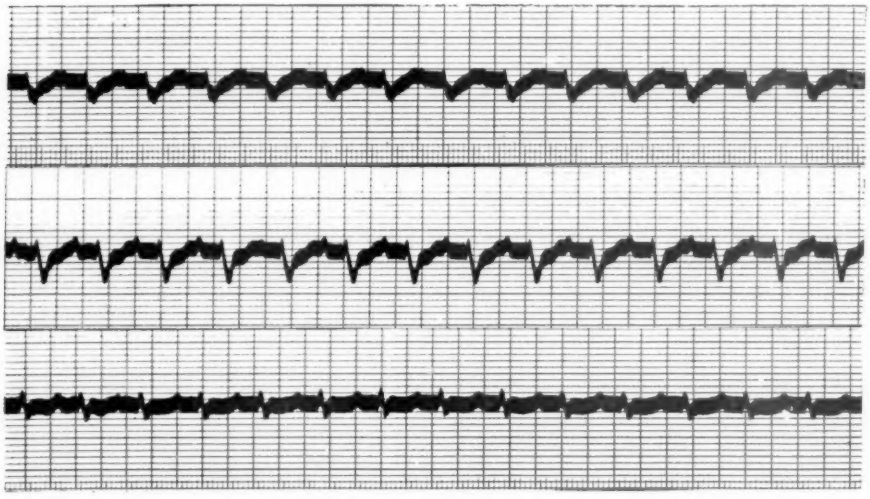

Fig. 14.—Case 6. Record taken the day before death shows inverted ventricular complexes in Leads I and II, delayed QRS interval, and indefinite T-waves.

An electrocardiogram taken on the seventh hospital day shows simple tachycardia, rate 128. The P-R interval is 0.2 second. The QRS complexes are inverted in Leads I and II; the amplitude is low and interval prolonged, though it is difficult to measure because it is indefinite. T-waves are also indefinite (Fig. 14).

DISCUSSION

The electrocardiograms from six cases of diphtheria are presented, showing delayed intraventricular conduction from 0.12 to 0.18 second. Definite notching of the QRS complexes is seen in each case. Cases 3, 4, and 5 (Figs. 8, 11, and 13) show right bundle-branch block. In the first, complete clinical and electrocardiographic recovery was observed; in the second, partial recovery was seen electrocardiographically and practically complete recovery clinically reported, while the third case terminated fatally. Case 1 suggests right bundle-branch block but is not typical because the T-wave in Lead I is upright. Cases 2 and 6 show marked intraventricular block. The QRS complexes are all upright with T-waves inverted in the first instance and voltage low and T-waves not definitely distinguishable in the latter instance.

The second case of this series showed an abnormal rhythm, which is interpreted as a nodal rhythm interrupted by auricular extrasystoles. Three days later normal P-R sequence was seen, and the rhythm was regular except for occasional auricular extrasystoles. Thereafter a regular mechanism prevailed until discharge. Normal mechanism was present in all the other cases. This might be explained by the fact that all cases associated with auriculo-ventricular block form the basis for another study and have been considered in the previous article.

Of the six cases studied, three were followed to electrocardiographic and clinical recovery. (The first case died of intercurrent infection after recovery from diphtheria.) One showed partial recovery before it was removed from our observation, and two terminated fatally at the height of electrocardiographic disturbance.

Intraventricular block is a group term suggested by Oppenheimer and Rothschild[2] to include arborization block and bundle-branch block, and is characterized by delay in the QRS interval. These authors reported a series of cases revealing at autopsy extensive fibrosis of the endocardial surfaces of the ventricles, which they called arborization block. The electrocardiograms showed delayed QRS conduction, low voltage, and absence of typical diphasic curves with large T-waves opposite in direction to that of the initial ventricular deflection of bundle-branch block. Bundle-branch block indicates a lesion of a branch of the conduction system below the bifurcation. The electrocardiograms under these circumstances show delayed QRS conduction with notching. The ventricular complexes are of large amplitude and diphasic with the T-wave opposite in direction to that of the initial deflection.

Numerous observers have reported delayed intraventricular block or bundle-branch block as transient phenomena. Robinson[3] has reported cases showing intraventricular conduction defects which disappeared with functional improvement of the heart. During the height of the disturbance and when the heart action was irregular, the beats follow-

ing long diastolic pauses were more nearly normal than those following short pauses. The element of rest and recovery in these cases, consequently, played an important part in conduction defects.

Willius and Keith[4] described three cases of incomplete bundle-branch block associated with myocardial disease. All showed a normal electrocardiogram with clinical recovery, so that the authors concluded that profound disturbances in ventricular conduction may be evanescent with or without cardiac decompensation. Leinbach and White[5] described a patient with a normal electrocardiogram and a slow rate at rest and right bundle-branch block during a rapid rate after exercise. Another patient showed alternate complexes of right bundle-branch block and normal mechanism before the branch block became permanent. Intraventricular conduction defects probably dependent upon functional depression were described by Wilson and Herrmann[6] in a case of uremia shortly before death. Colvin[7] described a similar case in carbon monoxide poisoning, followed by recovery.

The occurrence of intraventricular conduction defects in the course of diphtheria followed by electrocardiographic recovery, indicates that these phenomena may result from toxic depression of the conduction system.

SUMMARY

Six cases of diphtheria are presented in which delayed intraventricular conduction was observed. In four instances this was a transient phenomenon followed by electrocardiographic recovery.

The author wishes to express his appreciation to Dr. J. A. Toomey and the Department of Contagious Diseases for permission to study these cases.

REFERENCES

1. Stecher, Robert M.: Electrocardiographic Changes in Diphtheria. I. Complete Auriculoventricular Dissociation, Am. Heart J. **4**: 545, 1929.
2. Oppenheimer, B. S., and Rothschild, Wm. A.: Electrocardiographic Changes Associated With Myocardial Involvement, J. A. M. A. **69**: 429, 1917.
3. Robinson, G. C.: Relation of Changes in Form of Ventricular Complex of Electrocardiogram to Functional Changes of the Heart, Arch. Int. Med. **18**: 830, 1916.
   Significance of Abnormalities in Form of Electrocardiogram, Arch. Int. Med. **24**: 422, 1919.
4. Willius, F. A., and Keith, N. M.: Intermittent Incomplete Bundle-Branch Block, Am. Heart J. **2**: 255, 1927.
5. Leinbach, R. F., and White, P. D.: Two to One Right Bundle-Branch Block, Am. Heart J. **3**: 422, 1928.
6. Wilson, F. N., and Herrmann, G. R.: Some Unusual Disturbances of the Mechanism of the Heart Beat, Arch. Int. Med. **31**: 921, 1923.
7. Colvin, L. T.: Electrocardiographic Changes in a Case of Severe Carbon Monoxide Poisoning, Am. Heart J. **3**: 484, 1928.

A COMPARISON OF RECORDS TAKEN WITH THE EINTHOVEN STRING GALVANOMETER AND THE AMPLIFIER-TYPE ELECTROCARDIOGRAPH*

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Dock[1] recently has reemphasized the distortion of the electrocardiogram which results from introducing a condenser in series with the leads from a patient to the string galvanometer and has made this phenomenon the premise for a critical analysis of records obtained with electrocardiographs of the resistance-and-capacitance-coupled amplifier type. He presents an illustration showing distortion of the S-wave, S-T interval, and T-wave produced by the amplifier-type instrument due to overshooting of the terminal part of the QRS deflection, and he states that this distortion increases with increase in duration and voltage of the QRS complex. Another illustration shows overshooting of the base line in the amplifier standardization record. In conclusion he states that although the distortion is slight in most records it must be considered in interpreting the tracings, and that electrocardiograms made in this manner can accurately duplicate Einthoven string galvanometer records only when the standardizing test current does not produce overshooting on the "break." For these reasons he considers the amplifier-type instrument unsatisfactory.

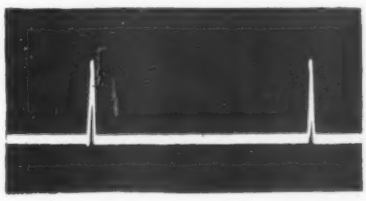

Fig. 1.—A standardization record of the amplifier-type electrocardiograph.

No other data on the accuracy of records obtained by electrical amplification of the heart currents are available. Because of this and the increasing popularity of the amplifier-type electrocardiograph, the Einthoven string galvanometer and amplifier records of twenty-five patients have been compared by detailed inspection and measurement. The amplifier-type instrument used was a late model of the Victor electrocardiograph, and the string galvanometer was a new Cambridge-Hindlé model number two. The tracing on one instrument was taken immediately after that on the other, each apparatus being used first

*From the Research Laboratories, Beth Israel Hospital, and the Department of Medicine, Harvard Medical School, Boston.

TABLE I

NAME	AGE	DIAGNOSIS	LEAD	RATE HINDLE	RATE VICTOR	P-R HINDLE	P-R VICTOR	QRS HINDLE	QRS VICTOR	Q-T HINDLE	Q-T VICTOR
W.M.	17	Normal	1	81	79	0.12	0.12	0.08	0.08	0.36	0.36
			2	77	77	0.12	0.12	0.09	0.09	0.36	0.37
			3	77	78	0.12	0.12	0.09	0.09	0.35	0.35
W.R.	40	Normal	1	66	66	0.16	0.17	0.08	0.08	0.37	0.38
			2	63	66	0.20	0.20	0.08	0.08	0.39	0.36
			3	66	64	0.19	0.20	0.09	0.09	0.36	0.36
P.D.	20	Normal	1	82	89	0.12	0.15	0.07	0.07	0.32	0.32
			2	82	86	0.14	0.14	0.10	0.09	0.34	0.35
			3	79	84	0.12	0.12	0.10	0.10	0.35	0.34
C.M.	34	Normal	1	87	91	0.15	0.15	0.08	0.08	0.32	0.32
			2	80	84	0.15	0.16	0.08	0.08	0.34	0.34
			3	77	87	0.15	0.15	0.08	0.08	0.33	†
A.D.	28	Mitral stenosis	1	73	73	0.38	0.38	0.08	0.08	0.30	0.30
			2	74	73	0.34	0.34	0.08	0.08	0.30	0.30
			3	74	74	0.32	0.32	0.08	0.08	0.32	0.32
I.D.	15	Mitral stenosis	1	99	95	0.20	0.21	0.10	0.10	0.32	0.32
			2	102	99	0.20	0.21	0.10	0.10	0.32	0.32
			3	96	102	0.20	0.21	0.10	0.09	0.33	0.32
M.A.	27	Normal	1	75	73	0.15	0.15	0.08	0.07	0.35	0.35
			2	77	77	0.16	0.16	0.08	0.08	0.35	0.35
			3	78	77	0.16	0.16	0.08	0.08	0.34	0.33
A.E.	27	Normal	1	49	50	0.16	0.16	0.08	0.08	0.41	0.41
			2	48	55	0.16	0.16	0.11	0.11	0.42	0.42
			3	46	48	0.16	0.16	0.12	0.12	0.42	0.42
B.J.	24	Normal	1	75	74	0.16	0.16	0.08	0.08	0.32	0.32
			2	80	72	0.14	0.14	0.09	0.09	0.36	0.36
			3	78	74	0.15	0.14	0.08	0.08	0.35	0.36
S.E.	55	Normal	1	60	61	0.14	0.14	0.12	0.12	0.36	0.36
			2	65	63	0.15	0.15	0.12	0.11	0.37	0.37
			3	62	60	0.15	0.15	0.11	0.11	0.37	0.37
R.R.	24	Aortic regurgitation Mitral stenosis	1	116	121	0.20	0.20	0.08	0.08	0.28	0.28
			2	121	125	0.19	0.19	0.10	0.09	0.30	0.30
			3	116	121	0.20	0.20	0.10	0.09	0.31	0.30
B.G.	50	Angina pectoris	1	58	70	0.11	0.11	0.09	0.09	0.42	0.42
			2	60	62	0.12	0.12	0.10	0.10	0.44	0.44
			3	58	62	0.13	0.12	0.09	0.09	†	†
S.G.	58	Angina pectoris	1	68	67	0.13	0.14	0.11	0.10	†	†
			2	68	68	0.13	0.14	0.10	0.10	0.39	0.39
			3	70	70	†	†	0.10	0.10	0.38	0.39
N.F.	38	Secondary anemia	1	80	82	0.17	0.16	0.07	0.07	0.33	0.33
			2	81	81	0.17	0.17	0.09	0.08	0.33	0.32
			3	79	81	0.16	0.16	0.07	0.07	0.30	0.30
S.S.	76	Aortic regurgitation	1	80	81	0.20	0.21	0.07	0.07	0.30	0.30
			2	77	91	0.23	0.23	0.09	0.09	0.32	0.33
			3	72	73	0.22	0.22	0.09	0.09	†	†
J.S.	42	Bronchiectasis	1	96	97	0.11	0.11	0.07	0.07	0.32	0.32
			2	93	86	0.13	0.13	0.08	0.08	0.34	0.34
			3	87	97	0.13	0.13	0.08	0.08	†	†
I.P.	44	Essential hypertension	1	81	76	0.10	0.10	0.08	0.08	0.38	0.38
			2	81	81	0.12	0.13	0.06	0.06	0.38	0.38
			3	80	77	0.12	0.13	0.08	0.08	0.38	0.38
M.S.	26	Normal	1	79	79	0.15	0.14	0.07	0.08	0.32	0.32
			2	83	78	0.14	0.15	0.10	0.10	0.35	0.34
			3	81	75	0.14	0.14	0.10	0.10	0.34	0.34

TABLE I

DURATION P		AMPLITUDE P		AMPLITUDE Q		AMPLITUDE R		AMPLITUDE S		AMPLITUDE T	
HINDLE	VICTOR	HINDLE	VICTOR	HINDLE	VICTOR	HINDLE	VICTOR	HINDLE	VICTOR	HINDLE	VICTOR
0.09	0.08	0.7	0.6	0.0	0.0	5.5	4.3	3.5	2.7	1.8	1.7
0.10	0.09	2.2	1.8	2.3	2.0	20.0	16.5	4.1	3.0	4.5	3.5
0.09	0.09	1.5	1.3	3.5	3.0	19.2	15.5	3.0	1.8	2.0	1.8
0.08	0.08	1.0	0.9	0.2	0.2	7.7	6.0	1.5	1.2	2.3	2.0
0.12	0.12	1.5	1.3	0.1	0.1	8.8	7.3	3.5	2.8	2.8	2.4
0.08	0.08	0.7	0.7	1.8	1.3	1.7	1.7	2.2	2.0	0.5	0.5
0.07	0.08	1.1	1.0	0.0	0.0	6.0	5.2	0.2	0.2	2.8	2.0
0.09	0.10	1.3	1.0	0.0	0.0	7.8	6.3	5.0	4.3	4.5	3.5
0.08	0.07	*0.3	*0.2	0.7	0.8	1.7	1.3	5.0	4.3	1.7	1.4
		−0.5	−0.5								
0.08	0.08	0.8	0.7	0.4	0.6	9.0	8.0	0.7	0.2	2.5	1.8
0.09	0.10	1.6	1.5	1.0	1.0	10.0	9.0	0.8	0.8	2.5	2.0
0.09	0.09	0.8	0.8	0.3	0.5	4.2	3.0	0.2	0.2	0.3	†
0.12	0.12	1.9	1.6	0.1	0.1	4.8	4.2	7.0	5.0	1.0	0.9
0.11	0.11	*2.0	*1.8	1.0	1.0	9.0	9.0	2.2	2.0	1.3	1.2
		0.5	0.5								
0.10	0.10	−0.4	−0.4	3.0	2.5	11.0	10.2	0.3	0.3	0.3	0.3
0.08	0.09	0.8	0.9	0.0	0.0	8.0	7.0	1.2	1.0	1.3	1.3
0.12	0.12	1.5	1.2	0.0	0.0	18.8	17.3	0.0	0.0	1.5	1.5
0.08	0.08	0.5	0.5	1.0	1.0	12.0	12.0	0.0	0.0	0.3	0.3
0.08	0.09	1.2	0.9	1.0	1.0	8.8	6.4	1.0	0.7	3.0	2.0
0.09	0.09	2.0	1.5	0.6	0.5	12.2	10.7	1.8	1.7	4.0	3.3
0.09	0.09	1.2	1.0	0.7	0.7	4.8	4.5	1.0	1.0	1.5	1.5
0.08	0.08	0.8	0.7	0.0	0.0	6.0	4.7	0.5	0.4	3.2	2.7
0.09	0.09	1.0	0.9	1.5	1.3	17.3	15.0	1.9	1.3	5.4	4.3
†	†	†	†	1.5	1.2	12.5	11.0	1.2	1.0	2.2	1.6
0.10	0.10	0.9	0.8	0.0	0.0	3.7	3.4	2.7	2.7	2.8	2.4
0.10	0.10	1.3	1.1	0.8	1.0	16.0	15.0	1.6	1.3	5.8	5.2
0.08	†	0.8	0.5	1.0	0.9	16.0	14.6	0.0	0.0	3.0	2.8
0.06	0.06	0.3	0.4	3.0	2.5	7.5	7.2	4.0	3.3	3.3	3.2
0.09	0.09	2.0	1.6	1.0	1.0	12.0	10.0	3.0	2.5	6.0	5.5
0.09	0.09	1.7	1.2	0.0	0.0	6.0	5.5	1.7	2.0	3.4	2.7
0.11	0.11	2.0	1.8	2.0	1.8	12.0	10.8	0.0	0.0	1.0	1.0
0.12	0.12	3.2	2.7	0.2	0.2	15.0	13.0	0.3	0.3	1.6	1.4
0.11	0.11	1.2	1.2	1.0	0.7	13.3	12.0	8.0	7.3	0.8	0.8
0.06	0.06	0.8	0.8	0.4	0.4	1.2	1.2	1.2	1.1	1.1	1.1
0.09	0.09	0.8	0.8	0.6	0.8	5.8	5.7	1.8	1.7	1.5	1.4
0.06	0.06	0.2	0.2	0.2	0.2	4.8	4.7	0.7	0.7	0.3	0.3
0.10	0.09	1.0	1.0	2.4	2.2	12.2	11.8	1.4	1.3	*−1.0+0.4	*−1.0+0.4
0.10	0.10	1.2	1.2	4.8	4.4	4.0	3.3	2.7	2.3	*−1.0+0.3	*−1.0+0.3
†	†	†	†	0.0	0.0	0.0	0.0	9.0	9.0	−1.2	−1.2
0.10	0.10	1.2	1.0	0.0	0.0	7.4	7.0	0.5	0.5	1.7	1.7
0.10	0.10	1.3	1.1	0.3	0.3	9.4	9.2	0.0	0.0	1.2	1.0
0.10	0.10	0.4	0.4	1.0	1.0	3.6	3.0	0.0	0.0	0.5	0.5
0.08	†	0.6	0.7	0.0	0.0	9.0	7.2	0.0	0.0	1.3	1.2
0.09	0.10	1.5	1.3	0.0	0.0	6.3	6.2	6.0	5.0	1.2	1.2
0.07	0.07	0.8	0.8	0.0	0.0	3.6	3.0	13.0	11.2	−0.3	−0.3
0.08	0.08	1.3	1.1	0.2	0.2	9.5	9.0	0.0	0.0	1.5	1.5
0.10	0.10	1.5	1.2	0.6	0.0	6.2	7.0	1.0	0.8	1.8	1.8
0.07	0.07	0.6	0.5	4.8	4.8	1.0	1.0	0.6	1.0	†	†
0.06	0.06	1.4	1.3	3.0	3.0	19.0	18.6	0.0	0.0	2.7	2.0
0.08	0.08	1.3	1.2	1.0	0.8	10.0	10.0	0.0	0.0	1.9	2.0
0.08	0.08	*+0.8−0.7	*+0.7−0.7	0.0	0.0	2.3	2.2	14.0	13.7	−1.0	−1.0
0.06	0.06	0.4	0.4	0.0	0.0	4.0	3.5	1.8	1.3	2.4	2.4
0.09	0.09	1.3	1.3	0.2	0.2	11.0	10.0	4.0	3.3	5.2	5.2
0.09	0.09	1.2	1.2	0.0	0.0	8.0	7.0	3.0	2.5	3.2	3.0

*Diphasic Wave.
†Indistinct.

TABLE I.—CONT'D

NAME	AGE	DIAGNOSIS	LEAD	RATE HINDLE	RATE VICTOR	P-R HINDLE	P-R VICTOR	QRS HINDLE	QRS VICTOR	Q-T HINDLE	Q-T VICTOR
G.S.	22	Normal	1	76	68	0.15	0.15	0.09	0.09	0.32	0.33
			2	67	67	0.14	0.14	0.10	0.10	0.34	0.35
			3	82	78	0.14	0.14	0.10	0.10	0.34	0.35
J.L.	21	Normal	1	77	72	0.16	0.17	0.08	0.08	0.34	0.34
			2	76	71	0.17	0.17	0.09	0.08	0.35	0.35
			3	72	70	0.16	0.16	0.08	0.08	0.35	0.35
L.R.	22	Normal	1	86	77	0.16	0.16	0.09	0.08	0.34	0.34
			2	81	75	0.15	0.16	0.08	0.08	0.36	0.34
			3	82	77	0.16	0.16	0.08	0.08	0.35	0.35
J.O.	31	Normal	1	72	69	0.16	0.17	0.08	0.08	0.36	0.36
			2	68	64	0.15	0.15	0.08	0.08	0.38	0.38
			3	63	62	0.15	0.15	0.09	0.09	0.38	0.37
D.G.	27	Normal	1	68	73	0.14	0.13	0.09	0.09	0.36	0.36
			2	78	73	0.18	0.18	0.10	0.10	0.36	0.37
			3	71	78	0.18	0.18	0.11	0.10	0.36	0.35
K.D.	65	Normal	1	82	87	0.12	0.12	0.09	0.09	†	†
			2	82	87	0.12	0.12	0.08	0.08	0.34	0.34
			3	82	86	0.13	0.13	0.09	0.09	0.34	0.34
W.G.	46	Normal	1	86	82	0.14	0.14	0.08	0.08	0.34	0.34
			2	87	85	0.15	0.15	0.06	0.06	0.34	0.34
			3	88	86	0.14	0.14	0.08	0.08	0.31	0.31

†Indistinct.

on approximately one-half the patients. All records were made with the patient supine, and no change in position was allowed during the shift from one electrocardiograph to the other. Skin resistance, as measured with the comparison circuit of the string galvanometer, was in no instance over two thousand ohms at the time of taking the tracing with this instrument, and in no record was there overshooting of the string. Particular attention was given in all instances to accuracy of standardization. Measurements were made with the aid of a reading glass, and the amplitude of all waves was checked by superimposing the two records of each patient. In tracings showing variations in voltage of a wave the maximum amplitude of each wave was recorded. The results of the study are presented in Table I.

No difficulty was experienced with overshooting of the base line in the standardization records of the amplifier-type instrument. A typical standardization is shown in Fig. 1. The time relationships (P-R, QRS and Q-T intervals) of the records obtained with the two electrocardiographs were practically identical throughout, and the amplifier tracings accurately duplicated all the finer details of waves recorded by the string galvanometer. In no instance did the amplifier records show overshooting of the terminal part of the QRS deflection with consequent distortion of the S-T interval and T-wave. Fig. 2 shows no overshooting of the QRS in a patient with waves of increased amplitude.

Amplitude of Deflections.—The measurements of height of the various waves showed small but distinct differences in the records obtained with the two instruments. In the majority of instances, however, the dif-

TABLE I.—CONT'D

DURATION P		AMPLITUDE P		AMPLITUDE Q		AMPLITUDE R		AMPLITUDE S		AMPLITUDE T	
HINDLE	VICTOR	HINDLE	VICTOR	HINDLE	VICTOR	HINDLE	VICTOR	HINDLE	VICTOR	HINDLE	VICTOR
0.09	0.09	0.3	0.3	0.0	0.0	5.2	5.0	1.0	0.8	2.0	2.0
0.10	0.10	1.3	1.2	1.4	1.3	12.8	12.8	1.5	1.3	3.7	3.7
0.09	0.09	1.2	1.0	1.4	1.3	10.6	10.0	1.6	1.0	2.2	2.2
0.08	0.08	1.0	0.8	0.1	0.1	10.0	8.2	2.5	2.1	3.6	3.4
0.09	0.09	1.6	1.3	3.0	2.6	20.8	18.2	0.0	0.0	5.0	4.6
0.08	0.09	1.0	0.9	2.8	2.3	13.2	12.2	0.0	0.0	1.9	1.4
0.08	0.08	0.9	0.8	1.0	0.7	9.0	7.2	1.0	1.0	2.3	2.3
0.09	0.09	1.3	1.0	0.3	0.3	9.0	8.2	1.3	1.0	3.4	3.4
0.08	0.08	0.8	0.8	0.0	0.0	2.5	1.7	1.7	2.0	1.3	1.3
0.09	0.10	1.2	0.9	0.0	0.0	6.7	5.7	8.0	7.0	2.7	2.2
0.09	0.09	2.0	1.7	0.5	0.5	9.7	9.0	0.7	0.5	4.8	4.5
0.09	0.09	−0.8	−0.8	2.2	2.0	13.8	13.2	0.0	0.0	2.7	2.2
0.06	0.06	1.0	0.9	0.5	0.5	8.2	7.0	0.8	0.3	3.4	2.7
0.11	0.10	2.0	1.8	0.0	0.0	7.2	5.5	3.0	2.4	4.5	3.4
0.08	0.08	1.6	1.4	0.0	0.0	1.3	1.1	2.2	2.0	1.2	1.2
0.08	0.08	1.4	1.4	1.4	1.2	9.7	9.2	0.0	0.0	0.2	0.3
0.07	0.07	1.3	1.1	0.0	0.0	7.8	7.2	4.2	4.2	3.2	3.0
0.08	0.08	*+0.4−0.7	*+0.4−0.7	0.0	0.0	4.0	3.7	6.5	6.2	4.0	3.0
0.08	0.08	1.0	1.0	0.0	0.0	11.8	11.8	0.5	0.5	2.0	2.0
0.09	0.09	1.3	1.2	0.0	0.0	9.2	8.0	0.2	0.2	3.0	2.8
0.08	0.08	0.5	0.6	0.0	0.0	0.0	0.0	3.0	4.0	1.3	1.0

*Diphasic wave.

ferences observed were of no practical significance. The P-waves in either two or three leads of the amplifier records of eighteen patients were slightly lower than in the string galvanometer tracings. The diminution in amplitude ranged from 0.1 to 0.5 mm. In over one-fourth of the leads the waves were of the same height, while in approximately one-half there was a diminution of 0.1 or 0.2 mm. The P-wave in one lead of four amplifier records was slightly higher than in the corresponding string galvanometer tracings. A large majority of the Q-waves were of the same amplitude in the two types of electrocardiograms, although with waves of rather large amplitude a diminution in the amplifier records amounting to as much as 0.5 mm. was observed. In two leads of one record and in a single lead of three others the Q-wave in the amplifier tracing was 0.1 or 0.2 mm. higher than in the string galvanometer curves. Differences in height of the R-waves ranging from zero to 3.7 mm. were observed, two-thirds of the amplifier leads showing diminutions of less than 1.1 mm. In only one lead of a single record was the R-wave higher in the amplifier than in the string galvanometer tracing. The S-waves of the amplifier records showed a diminution in height ranging from zero to 2 mm., there being no difference in over one-third of the leads and differences of 0.1 to 0.5 mm. in another one-third. In four tracings the S-wave of the amplifier records was higher in one lead than in the string galvanometer curves, the difference amounting to 0.3 to 1 mm. The T-waves in the amplifier records showed diminished amplitude ranging

from zero to 1.1 mm. with nearly one-half of the tracings showing a difference of zero or 0.1 mm. In one lead of two records, the T-wave of the amplifier curve was 0.1 mm. higher than in the string galvanometer tracing. Throughout the measurements of amplitude it was ob-

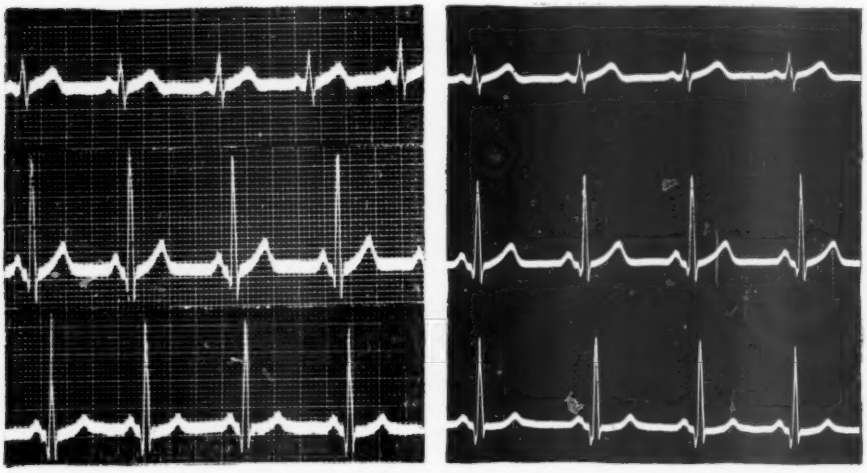

Fig. 2.—String galvanometer and amplifier electrocardiograms of a patient with waves of increased amplitude. Note absence of overshooting of terminal part of the QRS complex and accurate duplication of notching of descending limb of the R-wave in Lead I. All waves of the amplifier record are of diminished amplitude, the difference being most marked in the R-wave of Leads II and III.

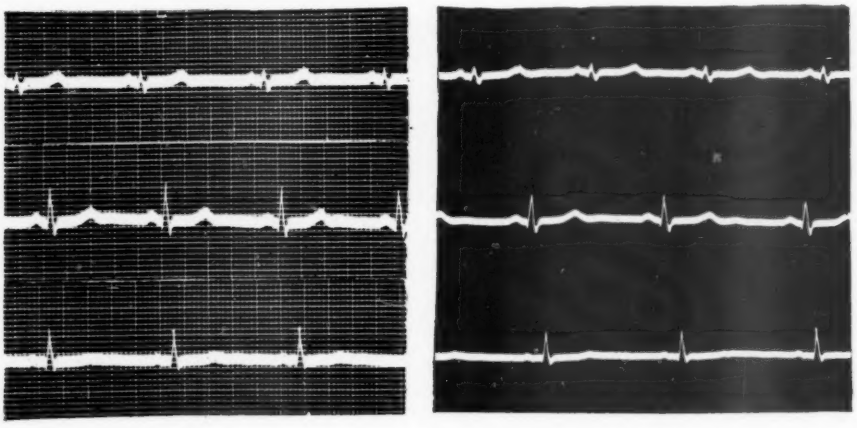

Fig. 3.—String galvanometer and amplifier electrocardiograms of low normal voltage showing practically no difference in height of any wave in the two records.

served that the differences in the two types of records tended to be greater in waves of higher voltage. Fig. 3 shows practically no difference in height of any wave in the two records of a patient with complexes of low normal voltage; while in Fig. 2, with waves of increased amplitude, the amplifier deflections are diminished.

CONCLUSIONS

The string galvanometer and amplifier-type electrocardiograms of twenty-five patients have been compared.

The time relationships and the finer details of all waves were accurately recorded by the amplifier-type instrument. No difficulty was experienced with overshooting of the base line of the standardization record or with overshooting of the terminal part of the QRS deflection.

With the exception of the Q-wave the deflections in the amplifier records were usually of slightly less amplitude than in the string galvanometer tracings. In all waves the difference in amplitude tended to be greater in complexes of higher voltage, but only occasionally did the difference assume a practically significant magnitude. No attempt was made to find a theoretical explanation for the differences observed.

Since the curves obtained with the amplifier-type instrument were essentially the same as those recorded by the string galvanometer, except for the slight differences in amplitude, they may be considered satisfactory.

REFERENCE

1. Dock, W.: The Distortion of the Electrocardiogram by Capacitance, a Critical Analysis of the Electrical Amplification of Heart Currents, AM. HEART J. 4: 109, 1928.

VEGETATIVE ENDOCARDITIS DUE TO THE BRUCELLA MELITENSIS*

With a Case Report

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INTRODUCTION

WITHIN the past few years the medical literature of this country has been reporting increasing numbers of cases of undulant fever, more commonly designated as Malta fever. However, due to the low mortality rate of the disease in the United States, practically none of the reports include necropsy findings. This is in distinct contrast to European reports, particularly those from the Mediterranean countries, where the malady is more prevalent and of greater virulence. Then, too, in most of the cases of undulant fever now being reported in this country, the causative agent is the Brucella melitensis, variety abortus, or even the Brucella abortus (Bang) itself. However, in the goat-raising districts of the southwestern part of the United States, Malta fever due to the true melitensis species is endemic. The first epidemic of the malady that has ever been recorded in the United States occurred in that section of the country in 1922.[1] Most of the European cases are due to the Brucella melitensis, variety melitensis A, the organism found in the present case.[2]

In Carpenter's statistical report of 18 cases of undulant fever which occurred in New York State during the year ending June, 1927, 17 showed evidence of Br. abortus infection, while the remaining case, which incidentally is the present one, showed the Br. mellitensis A.[3] Evans, in a recent review of 20 cases of undulant fever reported in the United States, gave the abortus variety as the causative organism in all 20 instances.[4] In 1918 the same observer pointed out the very close biological and serological relationship between these organisms; in fact, so intimately are they related that they cannot be distinguished by ordinary laboratory tests.[4, 5] A slight but definite distinction between the two varieties may be detected by the agglutinin absorption test.

After a survey of the literature, we were unable to find recorded any fatal cases, with necropsy findings, of subacute bacterial endocarditis due to the Br. melitensis, variety melitensis A, in this country. In

*From the Third (New York University) Medical Division and the Pathological Laboratories, Bellevue Hospital, New York City. Read (in abstract) before the New York Pathological Society, Jan. 10, 1929, and published in the Archives of Pathology, May, 1929.

1926 Moore and Carpenter reported a fatal case of subacute bacterial endocarditis due to the Br. abortus from the Second (Cornell) Medical Service of Bellevue Hospital which at necropsy showed a vegetative endocarditis implanted on an old deformed aortic valve.[6] Recently Scott and Saphir reported a case of Br. melitensis, variety abortus, bacteremia associated with endocarditis. However, they stated that there was no proof in their case that the endocarditis was caused by the brucella infection.[7] They believed that their case was one of an acute and chronic endocarditis associated with Br. melitensis (abortus) bacteremia rather than one of endocarditis caused by the brucella itself.

In view of these facts, it seems justifiable to place on record the following case which was observed clinically and which came to necropsy.

REPORT OF CASE

T. G., a white male 38 years old, born in Italy, and a laborer by occupation, was admitted to Bellevue Hospital, Third (New York University) Medical Service, on December 8, 1926, complaining of fever.

Previous history.—His family history was irrelevant. The patient served in the Italian army during the World War, during which time he received typhoid inoculations. He did not recall having had any childhood diseases. In 1916 he had malaria. In 1917 swollen glands of the neck were removed. While in Italy in March, 1926, one month before he came to the United States, the patient drank goat's milk.

Present illness.—In May, 1926, one month after arrival in this country, the patient was admitted to a hospital in New York City where a diagnosis of influenzal pneumonia was made. This diagnosis was later changed to typhoid fever after a positive Widal test was obtained. During his stay in this hospital he had a persistent temperature, an enlarged liver, a palpable spleen, and a systolic murmur was heard at the apex. He left the hospital early in September, 1926, against the advice of the physicians and went to the country. After feeling well for about three weeks, the patient began to have daily attacks characterized by chills lasting about twenty minutes, fever of from one to five hours duration, which was accompanied by profuse perspiration, and severe headaches. Concomitantly with these symptoms he experienced a sharp, more or less continuous pain across the small of the back which radiated around both upper quadrants of the abdomen. Somewhat later the patient developed a similar pain in the left buttock, and the heel of the left foot. Three weeks prior to admission to Bellevue Hospital, or about the middle of November, the small toe of the right foot became very painful, and he noticed that it was turning black.

Physical examination.—On admission the patient appeared chronically ill and seemed to have lost weight. He was slightly dyspneic but not orthopneic, and had an anxious expression on his face. His skin had a slight café au lait tint. The pupils reacted to light and accommodation. The conjunctivae were slightly bluish. The fundi oculi were normal. Many bad teeth were present. Several petechiae were seen on the under surface of the tongue. There was readily visible a purpuric rash over both lower extremities, most marked above the ankles. The small toe of his right foot was reddened, with some blackish discoloration, swollen, and extremely tender to touch. Petechiae were present on the fourth toe, one being present as a splintering hemorrhage under the toenail. This toe was also extremely tender. Both feet were slightly edematous. His fingers presented a definite clubbing.

The veins of the neck were not dilated, but the carotid pulsations were somewhat exaggerated. A purpuric rash was visible on the anterior aspect of the chest wall. No substernal tenderness was elicited. There was an area of dullness at the left base with diminished fremitus, bronchovesicular breathing, increased voice sounds, and many moist râles. Infarction at the left lower lobe was considered. The apical beat of the heart was visible in the fourth space 9.5 cm. to the left of the median line which was just outside the midclavicular line. The first sound was of poor muscular quality. The pulmonic second sound was accentuated. There was present a distant, musical, systolic murmur, heard with maximum intensity at the apex and transmitted to the left. Another systolic murmur was heard at the aortic area. The rhythm was regular. The rate was 96. The systolic blood pressure was 90 mm.; diastolic 60 mm. The temperature was 101 degrees F. The spleen was palpable two fingers beneath the costal margin, with a firm, hard edge but not tender. The liver was palpable 10.5 cm. below the xiphoid and tender. No ascites was present.

Course.—During the patient's stay of approximately three weeks in the hospital, his temperature was irregular, not of the undulant type from which the disease received its name, and ranged from 99 to 104 degrees F. His pulse rate ranged between 80 and 120. Normal sinus rhythm prevailed throughout his illness.

Several days after admission, a tender, purplish-red spot was observed on the tip of the fourth finger of the right hand at the edge of the nail. This was interpreted as being an Osler's node. A week later this had disappeared, as had also the one on the fourth toe of the right foot. Some ecchymoses of the small toe of this foot were still visible, but the tenderness had disappeared.

X-ray examination of the chest on Dec. 13, five days after admission, revealed congestion at the right base adjacent to the heart, which organ was enlarged to right and left. On Dec. 29, three weeks after admission, the patient complained of pain in his right thigh anteriorly. Tenderness was not marked over this area, but the femoral pulse in this leg was scarcely palpable. Early in the morning of Dec. 31 the patient suddenly cried out with pain in his groins. This subsided by four o'clock under the effect of morphia. At 5 A.M. he complained of severe pain in the lower abdomen. His skin became cold and clammy. Death took place one hour later.

The clinical diagnosis was as follows: I. Malta fever (undulant fever); II cardiac disease; (a) bacterial, active, Br. melitensis A., (b) endocarditis, subacute, (c) regular sinus rhythm, (d) class 3.

Laboratory Data.—On admission the patient had 3,930,000 red blood cells with 48 per cent hemoglobin; the white blood cells numbered 3,350 with 69 per cent polymorphonuclear neutrophiles and 26 per cent lymphocytes. Twelve days later the count was 2,600,000 red cells with 55 per cent hemoglobin and 1,800 white cells with 66 per cent polymorphonuclears and 34 per cent lymphocytes. A few days before death the cell counts were about the same as the second one. The Wassermann was negative. The first urine examination revealed the following: dark amber, specific gravity 1016, acid reaction, one plus albumin, no glucose, many finely granular casts, moderate amount of pus and epithelial cells. An analysis two weeks later gave a similar result; close scrutiny failed to reveal the presence of red blood cells. The Mosenthal test showed fixation in the higher dilutions. The red test was 20 per cent in the first hour and 25 per cent in the second. Vital capacity readings averaged 1500 c.c. on four occasions. Electrocardiographic tracings were normal.

A blood culture taken the day following admission presented a growth of colonies four days later. The organism was identified as a very small gram-negative, nonmotile, bacterium, so small that its outline could not be clearly defined. This same organism was obtained a week later after five days of incubation, but the colonies

were much less numerous. These cultures, as well as serum obtained during life, were forwarded to Dr. Charles M. Carpenter of the Diagnostic Laboratory of the N. Y. State Veterinary College to whom we are greatly indebted for his very careful and detailed study. Dr. Carpenter reported the causative organism as being a true type of Brucella melitensis A.

Necropsy Report.—The body was that of an adult male, 165 cm. in length, of slender, well-developed frame, fairly good musculature and nutrition. The fingers were distinctly clubbed. The skin presented a tint distinctly comparable to that of café au lait. There were no petechial hemorrhages to be made out in the visible mucous membranes or in the skin, with the exception of the skin covering the under surface of the little toe of the right foot, where there were several brownish or reddish-brown, streak-like patches. In addition, there was a single splinter hemorrhage beneath the nail of the little toe and of the toe immediately next to it.

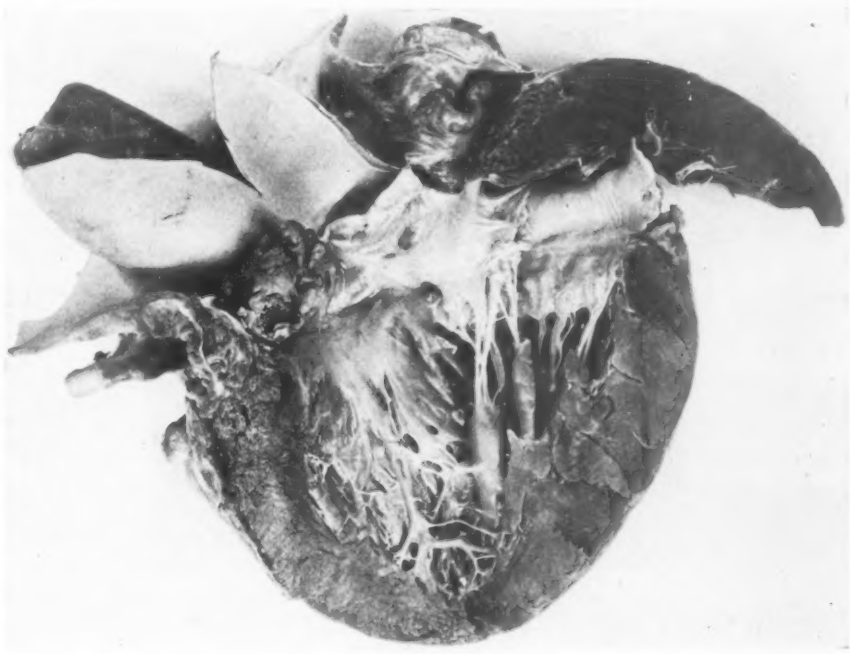

Fig. 1.—The two anterior aortic cusps are practically completely destroyed and replaced by a massive, friable vegetation. At about the center of the posterior cusp may be seen the remains of the small vegetation which broke off during necropsy.

On section, the subcutaneous fat and muscle tissues were well preserved and the peritoneum was smooth and glistening. The diaphragm was normally placed. The liver was distinctly enlarged, the lower edge reaching almost to the level of the umbilicus. The lower pole of the spleen projected beneath the costal slope on the left side for a distance of about 2 cm. Beneath the peritoneum in the right and lower portion of the abdomen was an enormous amount of bluish-red, apparently freshly clotted blood. The blood, on dissection, was found to occupy a space which could just about be covered by a large hand, extending from the right side of the lumbar spine outward and upward beneath the peritoneum to a point almost reaching the midline of the body anteriorly, and upward almost to the level of the lower border of the pancreas, and downward just to the level of the brim of the pelvis. The clot, on removal, weighed approximately 450 grams. Examina-

tion of the psoas magnus muscle failed to reveal any point of rupture and on section the muscle was not infiltrated by hemorrhage. At the same time, careful dissection of the mass, after removal, failed to show any sign of miliary aneurysm or any other anatomical cause for rupture.

Chest.—No thymic remains were visible. Both pleural cavities were fairly extensively obliterated by sheet-like adhesions which were broken down without great difficulty. The precordial area was large and the heart appeared to be floating. On opening the pericardium, fully 500 c.c. of perfectly clear straw-colored fluid escaped. The pericardium throughout was smooth and glistening.

Heart.—The heart appeared to be about normal in size. It weighed 345 gm. Both auriculoventricular openings were easily permeable, and the endocardium was excellently well preserved throughout, except for the two anterior aortic valves; these were practically completely destroyed and replaced by a solitary whitish or faintly cream-colored, granular mass of fused vegetations, irregularly round in shape, rather soft and friable, and approximating the size of one's thumb (Fig. 1).

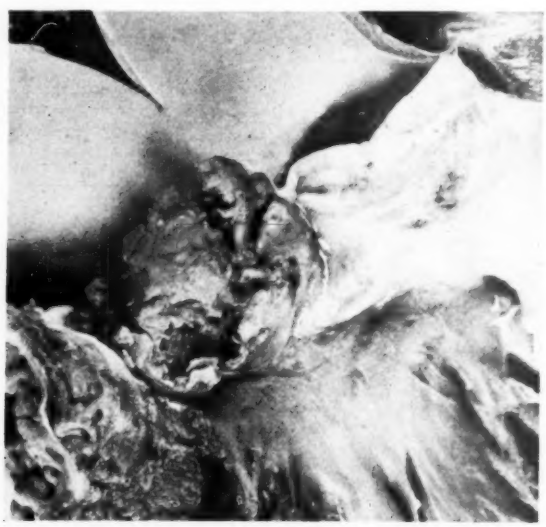

Fig. 2.—The two anterior aortic cusps are practically completely destroyed and replaced by a massive, friable vegetation. At about the center of the posterior cusp may be seen the remains of the small vegetation which broke off during the necropsy. (Part of heart shown in Fig. 1, showing details.)

The mass served apparently to completely block the aortic orifice. The posterior aortic valve was distinctly thickened, white in color and glistening, and on the ventricular surface, at about its center, presented a pea-sized vegetation which was of the same general appearance as that already described. This vegetation, however, was loosely attached and fell away apparently of its own weight. The heart muscle was pinkish in color, opaque, but otherwise apparently well preserved. The aorta was excellently well preserved.

Lungs.—The left lung, except for the adhesions mentioned above, a moderate amount of anthracosis, and some edema of the upper lobe, was apparently normal. The right lung was essentially the same as the left.

Spleen.—The spleen was massive, weighing 1035 gm., and measured 20 x 14 x 5 cm. It was bound to the under surface of the diaphragm and to the peritoneum externally by fibrous adhesions which in places were string-like, in other places sheet-like, but all of them were broken down without great difficulty. On removal,

the spleen presented a bluish-red appearance, and at the extreme upper pole were two wedge-shaped, cream-colored bodies, which lay apparently flush with the surface, were firm in consistency and, on sectic , extended downward for a distance of about 2 cm., presenting a perfectly smooth, yellowish surface and a distinctly reddish periphery. On the outer surface of the spleen, at about its center, was a somewhat rounded body which was about one centimeter in length on the surface, and which, on section, presented essentially the same naked eye changes as the infarctions at the upper pole. The splenic substance was diffusely bluish-red in color, somewhat opaque, rather more friable than in ordinary circumstances, and presented, scattered over the cut surface, moderate numbers of minute whitish specks, suggesting focal necroses or abscesses.

Kidneys.—The left kidney measured 15 x 7 x 3.5 cm. It was imbedded in a moderate amount of fat. The organ was distinctly enlarged, as indicated by its measurements; it cut without difficulty. The capsule stripped with ease and left behind an extensively and finely speckled surface. The speckling was due to the presence of numerous red points, between which the kidney substance showed as cream-colored islands, with here and there a pinpoint sized, sharply circumscribed, yellowish speck, corresponding apparently to miliary abscesses. The cortex bulged somewhat on section, and its markings were irregular. Scattered through the cortex were innumerable pinpoint sized red specks and moderate numbers of whitish or yellowish points, corresponding again, apparently, to abscesses. The right kidney measured 13 x 7 x 3.5 cm. and presented essentially the same naked-eye appearance as its fellow on the opposite side. The kidneys together weighed 530 gm.

Liver.—The liver was enormous, measuring 31 x 22 x 8 cm. and on removal weighed 2850 gm. Its surface was perfectly smooth, the capsule glistening. On section, the organ cut readily. The cut surface presented a pinkish background, scattered through which were numerous dull red specks, giving the organ as a whole a somewhat nutmeg appearance. Otherwise no focal lesions were visible in it. The substance was rather opaque, however, and a bit more friable than usual.

Lymph nodes.—Scattered throughout the retroperitoneal fat were moderate numbers of lymph nodes which varied in size from a few millimeters up to one centimeter. They appeared swollen and edematous, and presented a pinkish, opaque appearance. Some of them were finely speckled and occasionally one saw a minute white point, suggesting miliary abscesses.

The other organs were apparently normal on naked eye examination.

Anatomical Diagnosis.—1. Massive vegetative and ulcerative endocarditis of the aortic valves. 2. Massive septic splenomegaly with multiple anemic infarctions. 3. Subacute hemorrhagic nephritis. 4. Chronic parenchymatous degeneration of the liver. 5. Massive subperitoneal hemorrhage in right half of abdomen of unknown origin. 6. Subungual petechial hemorrhages in small toe and fourth toe of right foot. 7. Subcuticular hemorrhagic extravasations beneath the under surface of the right small toe.

Microscopic Examination.—Sections of the myocardium taken from various parts of both ventricles, presented slight lymphatic infiltration, consisting mainly of large and small round cells; no polymorphonuclear neutrophiles were seen. Moderate cloudy swelling and granular degeneration of the muscle fibers were also visible. A section through the large vegetation involving the right anterior aortic cusp showed a more or less homogeneous mass of granular and hyalinized material, fringed by a ragged edge from which pieces had apparently broken off. The base of the vegetation was directly continuous with the remains of the cusp, at which point organization had taken place. Gram-Weigert stain revealed no organisms in this massive vegetation.

The glomeruli of the kidneys showed beginning atrophy and infrequent hyalinization. Around some of them, within Bowman's capsule, were infiltrations of red blood cells and in many others infiltrations of small round cells around the capsules. A few presented moderately thickened Bowman's capsules. The tubules presented marked cloudy swelling and granular degeneration of the epithelium. An extravasation of red blood cells was visible in many of them. The arterial vessels were sclerotic and engorged.

Anthracosis and moderate congestion was seen in the lung sections.

The liver sections showed a marked degeneration around the central veins with pigment deposits; scattered islands of fat globules and a diffuse round cell infiltration were also visible.

Sections of the spleen presented marked congestion, scattered foci of necrosis, and a small area of anemic infarction.

COMMENT

The patient undoubtedly became infected in Italy by drinking goat's milk shortly before coming to the United States. The onset of his symptoms occurred about one month after his arrival, at which time he was admitted to a hospital where a diagnosis of influenzal pneumonia, which later was changed to typhoid fever, was made. In so far as both influenza and typhoid fever are two of a number of diseases which closely simulate undulant (Malta) fever, and because of the history of typhoid inoculations in the Italian army which might readily give a positive Widal reaction, the probability is that the fatal illness already manifested itself at that time.

The duration of the malady in this instance was, therefore, of about nine months simulating the subacute course of Streptococcus viridans endocarditis. Embolic phenomena as manifested by the petechiae and Osler's nodes, were obvious. The clubbing of the fingers, the enlarged spleen, and the café au lait tint of the skin completed the picture of a subacute bacterial endocarditis. Whether the endocardial lesion was the main seat of the disease might perhaps be questioned. However, it was the essential pathological lesion and undoubtedly caused by the Brucella melitensis.

The massive subperitoneal hemorrhage in the right half of the abdomen remains unexplained. The possibility of an embolic or mycotic aneurysm of a small peritoneal blood vessel which ruptured might be entertained, particularly in the presence of a large friable vegetation in the left side of the heart.

SUMMARY

A case of undulant (Malta) fever due to the Brucella melitensis, variety melitensis A, associated with a vegetative and ulcerative endocarditis of the aortic valves, and which clinically presented the manifestations of subacute bacterial (infective) endocarditis, is reported.

NOTE.—The necropsy was performed by Dr. Douglas Symmers, Director of Laboratories, to whom grateful acknowledgment is made for the courtesies extended.

REFERENCES

1. Watkins, W. W., and Lake, G. C.: Malta Fever With Special Reference to the Phoenix Ariz., Epidemic of 1922; Pub. Health Reports, **37**: 2895, 1922. Malta Fever in Southwestern United States, With Special Reference to an Outbreak in Phoenix, Ariz.; J. A. M. A. **89**: 1581, 1927.
2. Evans, A.: Studies on Brucella Melitensis, Hygienic Lab. Bull., No. 143, p. 10, 1925.
3. Carpenter, C. M., Parshall, C. J., and Baker, D. W.: Report of the Diagnostic Laboratory for the Year Ending June 30, 1927, Annual Report N. Y. State Vet. College, p. 52, 1926-1927.
4. Evans, A.: Human Infections With Organisms of Contagious Abortion of Cattle and Hogs; J. A. M. A. **88**: 631, 1927.
5. Ibid: Further Studies on Bacterium Abortus and Related Bacteria, J. Infect. Dis. **22**: 580, 1918.
6. Moore, V. A., and Carpenter, C. M.: Undulant Fever in Man Associated With Bacteria Indistinguishable From Brucella Abortus. Cornell Vet., p. 150, April, 1926.
7. Scott, R. W., and Saphir, O.: Brucella Melitensis (Abortus) Bacteremia Associated With Endocarditis. Am. J. M. Sc. **175**: 66, 1928.

Department of Reviews and Abstracts

Selected Abstracts

Perla, David, and Deutch, Max: The Intimal Lesion of the Aorta in Rheumatic Infections. Am. J. Path. 5: 45, 1929.

Two instances of macroscopic involvement of the aorta in recurrent rheumatic fever are described. A striking feature is the presence in one of the cases of an acute fibrinous lesion of the intima. The characteristics of the lesion are Aschoff bodies in the adventitia, perivascular infiltrations in the outer third of the media with destruction of elastic tissue and muscle elements, and recent and organized fibrinous plaques in the intima, the connective tissue cells comprising the vascular organization tissue having a characteristic vertical orientation at the base of the intimal lesions.

The authors believe that three groups of lesions may be distinguished in the aorta as the result of rheumatic fever. First, involvement of the adventitia tissues alone with perivascular infiltration and formation of Aschoff bodies. Second, involvement of the adventitia and the media. Third, involvement of all three layers of the aorta in either an acute or chronic process.

Taussig, Helen B.: A Case of Bundle-Branch Block Confirmed by Pathological Study. Bull. Johns Hopkins Hosp. 45: 40, 1929.

A case is reported in which there was a long-standing chronic rheumatic infection with severe myocardial damage. The first definite evidence of left bundle-branch block occurred only a few days before death.

The author has found in the literature reports of only eleven cases of complete bundle-branch block and one case of transient bundle-branch block that have been followed up by careful pathological study. Histological examination of the heart after preservation in formalin in the present case showed extensive scarring of the left branch of the His bundle and a very slight actual break in the continuity of the bundle. The bundle-branch block probably developed as one of the late manifestations of a long-standing cardiac disease. The pathological findings were in apparent accord with the clinical observations.

McIntosh, Rustin: The Determination of the Circulating Blood Volume in Infants by the Carbon Monoxide Method. J. Clin. Investigation 7: 203, 1929.

The technic is described for the determination in infants of the circulating blood volume by the carbon monoxide method based on the successful use of this method in tests on adults. In comparison with the dye method, the carbon monoxide method gave results which were more uniform and showed a fair conformity with body weight.

In a small series of determinations of blood volume in patients less than two years of age, the correlation of blood volume, body weight to surface area and to body length suggested a normal interrelationship of these measurements. As an estimate of the circulating blood volume in infants exclusive of the newborn group, the formula

$$\text{Blood Volume in c.c.} = (\text{Body Weight in Kg.}) \times (77 \pm 13)$$

may be expected to give the correct figure in more than half the cases.

Lloyd, W. D. M.: Action of Calcium on the Isolated Human Fetal Heart. J. Pharmacol. & Exper. Therap. **36**: 185, 1929.

The author has studied the action of calcium on two isolated human fetal hearts in perfusion experiments. As a result of addition of calcium salts to the perfusate, it was possible to show that there followed an increased strength of systole, a more regular rhythm, and better coordination between auricle and ventricle. At the end of one and one-half hours of perfusion all heart action finally ceased in systole of the ventricle.

Moon, R. O.: Some Observations on Diseases of the Myocardium. Brit. M. J., July 6, 1929, p. 1.

In this broad discussion of diseases of the myocardium the author presents the conventional views held on this subject. He divides the common types of myocardial disease into those due to fatty infiltration, fatty degeneration, fibroid heart muscle changes, and coronary obstruction. He discusses the diagnoses of patients with latent myocardial disease as well as those cases showing cardiac insufficiency. He indicates in series several points in the establishment of such a diagnosis. Under treatment the effect of climate, diet, and exercise are discussed.

McMillan, Thomas M., and Wolferth, Charles C.: An Untoward Effect of Barium Chloride in Producing Short Runs of Aberrant Ventricular Beats. J. Lab. & Clin. Med. **14**: 839, 1929.

A case is reported in which during six years of observation the patient had four attacks of complete A-V heart-block lasting for varying lengths of time up to two months. During the third attack barium chloride may have been a factor in restoring the sinus rhythm and preventing the onset of complete block again for eight months. During the fourth attack of complete block which lasted four months and ended in death, barium chloride failed to increase the effective ventricular rate in doses of 20 mg. four times a day and for four days. This dosage of the drug brought on a marked extrasystolic disturbance with frequent short runs of rapid ventricular tachycardia.

The disturbance is reported because the authors regard it as potentially serious and an untoward result of barium chloride and because the drug previously has been regarded as harmless in much larger doses than was required to bring about the disturbance in this case.

Master, Arthur M., and Oppenheimer, Enid Tribe: Obesity. J. A. M. A. **92**: 1652, 1929.

The authors have studied a series of 91 females and 8 males from an obesity clinic. The patients varied in age from ten to fifty-eight years, the greatest number being between thirty-five and fifty. The great majority did not have any ailments other than obesity. Blood pressures and pulse rates were studied at each visit, and in order to test the functional capacity of the circulatory system, a simple exercise tolerance test was also used.

The authors have noted that the obese person usually complains of dyspnea, fatigue, palpitation, dizziness, and headache. Sixty-seven per cent of the cases showed hypertension, and accelerated pulse rate was commonly present. In general, the more the overweight the greater the hypertension. With loss of weight the symptoms tend to disappear, and there is a corresponding fall in blood pressure

and pulse rate. With advancing years the blood pressure of obese patients increases. Apparently the longer the duration of the obese condition the higher the blood pressure.

Under thirty-three years of age the obese are somewhat more efficient than the average, suggesting that a moderate overweight in the young is a slight advantage.

The roentgenogram showed a sthenic or hypersthenic chest elevation of the diaphragm and an enlarged, widened heart with a hypertrophied ventricle and a hazy lower left border obscured by apical pericardial fat. With reduction in weight these characteristic signs disappear.

The electrocardiogram showed in 87 per cent a left ventricular preponderance. There was also noted a change in the P- and T-waves of the third lead. Sinus arrhythmia was common in this group of cases, occurring almost as frequently as ventricular preponderance.

The authors believe that it is clear from these studies that there exists in the obese person a distinct circulatory embarrassment, as proved by the abnormalities of the blood pressure, pulse rate, roentgenogram and electrocardiogram, and by the diminished capacity for work. It is not difficult to understand why the fat person is a poor surgical risk and why his mortality in pneumonia, nephritis, and heart disease is higher than the average. These factors give ample explanation for the distinct improvement commonly observed on reduction in weight in patients with valvular disease of the heart, hypertension, and coronary artery disease.

Bachmann, Harrold A.: Clinical Types of Edema in the Heart Failure of Childhood. Arch. Int. Med. 43: 795, 1929.

The author distinguishes two types of edema in children with cardiac disease. The first type is the commonly recognized dependent type involving the dependent portions of the body almost exclusively. It appears more prominently in the lower extremities, about the sacrum, and occasionally in other portions of the body. With this type of edema there is usually found ascites, marked enlargement of the liver, and other evidence of cardiac failure. As a rule, these children not only suffer from their discomfort and cardiac embarrassment but are also acutely ill and frequently toxic.

The second type of edema is generalized and corresponds to that seen in nephritis. It appears first in the face and later becomes equally prominent in all portions of the body. In degree it is never so overwhelming as that seen in nephrosis, but it has the same generalized distribution regardless of the position of the patient. Otherwise, the clinical picture is that of a patient with heart failure, though the heart failure is seldom so severe as that found in the previous type, nor is the patient ever so acutely ill. He appears more as a convalescent patient who has outlived an acute infection and presents the usually associated pallor and poor nutrition.

Response to treatment has shown a certain specificity which is of clinical value. In the dependent type of edema digitalis is of value while the addition of the milder diuretics aids little in hastening reabsorption and elimination. In the generalized type of edema, theobromine sodiosalicylate acts almost as a specific and usually without the aid of digitalis.

The type of lesion of the heart seems to influence little the kind of edema produced. It appears, however, that in the children whose history of heart failure is of recent date and whose hearts are, perhaps, still acutely infected, the edema associated with failure is more likely to be generalized. Dependent edema occurs almost exclusively in the patients with more chronic heart disease.

The prognosis of the patient with generalized edema is good, at least as to the immediate future, while that of the patient with the dependent type of edema is relatively bad.

Herxheimer, H.: Study of Heart Size in Olympic Athletes. Klin. Wchnschr. **8:** 402, 1929.

In an x-ray of the heart size of Olympic participators the author comes to the conclusion that the endurance sports, such as long distance running, bicycling, and skiing, all cause a definite heart enlargement in proportion to the body weight of the individual.

Danielopolu, D.: Control of an Attack of Angina Pectoris by Pressure Upon Carotid Sinus. Klin. Wchnschr. **8:** 596, 1929.

The author cites a case in which pressure upon the carotid sinus brought to an end an attack of angina pectoris. He believes that angina pectoris is precipitated by a pressor reflex, originating from "reflexogenic zones" in the heart, aorta, or carotid sinus and ending over the sympathetic pathway. By pressure upon the carotid sinus, it is possible that the same reflexogenic zone may originate a depressor reflex, ending over the parasympathetic pathway and thus bringing to an end the anginal attack.

Winternitz, M., and Selye, H.: A Case of Sinus Bradycardia Due to Arterial Thrombosis. Wien. Arch. f. inn. Med. **16:** 377, 1929.

In a patient sixty-two years of age, with generalized atherosclerosis and uremia, a terminal bradycardia (43-47 beats per minute) occurred. Serial sections of the heart revealed an old obliterating thrombus in the artery supplying the sino-auricular node.

MacMahon, H. E., and Burkhardt, E. A.: Meningococcus Endocarditis. Am. J. Path. **5:** 197, 1929.

A case of meningococcus endocarditis is reported with autopsy and bacteriological findings. The patient was a white woman, twenty-eight years old. The authors point out that it is important to remember that endocarditis can be caused by the meningococcus without any meningeal involvement and that such cases have been diagnosed as acute rheumatic fever with endocarditis or subacute bacterial endocarditis. They point out that the vegetations on the valve are rather typical, being large, firm, localized, and fungating with little tendency to discharge minute emboli. They believe that these organisms should be agglutinated and in some cases agglutinin absorption tests were performed in order properly to identify the meningococci. The literature pertaining to this subject is reviewed.

Hyland, C. M.: Meningococcus Endocarditis. J. A. M. A. **92:** 1412, 1929.

The meningococcus may be responsible for extrameningeal lesions and that these lesions need not necessarily be associated with infection of the meninges has been known for some years. The author reports the case of a man, aged forty-six, admitted to the hospital with shortness of breath, excessive perspiration, and cough. There was fever, signs of heart disease, leucocytosis, and positive blood cultures showing meningococci. The patient died twelve hours after admission. Vegetations were found on the aortic valve at autopsy.

Gold, Harry, and DeGraff, Arthur C.: Studies on Digitalis in Ambulatory Cardiac Patients. J. A. M. A. **92:** 1421, 1929.

It is shown in a study of patients that the therapeutic effects of digitalis may be induced in many cases by the daily repetition of such doses of the drug as the patient may eliminate daily after having been fully digitalized.

There has been included in this study also a note as to the behavior of digitalis in children as compared with adults. The authors have noted that the drug is less often seen to produce striking improvement in children because the type of heart failure relieved most effectively by digitalis is relatively common in heart disease among adults but relatively rare in children. In those cases in which less definite therapeutic effects are obtained, insufficient or excessive digitalization is more apt to occur because of the absence of a satisfactory guide to the intensity of digitalis action.

Cahan, Jacob M.: The Incidence of Heart Disease in School Children: J. A. M. A. **92:** 1576, 1929.

This report is based on the examination of 10,333 pupils in seven elementary schools, two junior high schools, and one senior high school for boys of Philadelphia. The purpose of the survey was to investigate the incidence, the morbidity, and the prophylaxis of organic heart disease in the children of these public schools. The total enrollment in the school was 11,578. Nine hundred and forty-three children who showed definite or suspicious signs of organic heart disease were reexamined. At this time the child's cardiac history was obtained. Fifty-eight were studied in the hospital or cardiac clinic. The number of patients with heart disease was 94, or 0.91 per cent; of this number 51 were boys, 43, girls.

The younger children had a slightly lower incidence of heart disease than the older pupils. Valvular disease, mitral stenosis, was the most frequent lesion found. This anatomic diagnosis was made in 53 of the 94 children with heart disease. Fourteen of these 53 showed signs of mitral stenosis and mitral insufficiency.

Consideration was given to three additional factors bearing on the prevalence of heart disease in school children; namely, (1) children with grave heart lesions unable to attend school; (2) children with crippled hearts attending special classes, and (3) children with definite or suspicious heart lesions that are being overlooked because of the inadequate routine examination of the clothed chest.

Rentschler, Edwin B., Vanzant, Francis R., and Rowntree, Leonard G.: Arthritic Pain in Relation to Changes in Weather. J. A. M. A. **92:** 1995, 1929.

This study was undertaken not to prove the relationship of arthritic pain to weather change but to determine whether or not such a relationship actually exists. In a group of 367 patients studied for a year, there was a positive relationship for 72 per cent of the time between the curve of pain and that of barometric pressure. For 21 per cent of the time the relation was equally definite, but as one line went up the other went down. In only 7 per cent of the time was a relationship undemonstrable.

For more than 90 per cent of the time there was a relation between the presence of storms and an increase of pain. Observations on humidity, temperature, and atmospheric electricity were inconclusive, although it is still possible that these agents working together have some effect.

The authors believe that many of the patients with arthritis can, with the increase of the severity of their pain, sense the approach or presence of storms. While this study has been confined to a group of patients with chronic arthritis, it is of importance in the study of climatic conditions in their relationship to rheumatism in general.

Yater, Wallace M.: Pathologic Changes in Auricular Fibrillation and in Allied Arrhythmias. Arch. Int. Med., **43:** 808, 1929.

A series of 145 cases of auricular fibrillation, 7 cases of auricular flutter, and 2 cases of paroxysmal tachycardia—all with necropsies—were studied from the stand-

point of etiology and pathology. All the usual types of heart disease were found, but cases of endocarditis and hyperthyroid states were the most numerous. Hypertension was found to be a common condition, but the occurrence of auricular fibrillation in other types of heart disease was uncommon. In about 8 per cent of the cases of auricular fibrillation, there was a combination of possible etiological factors and in about 9 per cent an etiological factor could not be suggested.

Twenty-nine hearts which had been the seat of these arrhythmias were studied microscopically. A distinctive lesion for the arrhythmia was not found and the lesions were not considered in themselves of sufficient importance to account for the arrhythmia. There apparently is not, therefore, a specific histological syndrome in auricular fibrillation and probably none in auricular flutter and paroxysmal tachycardia.

Rosenbluth, E., and Winterberg, H.: Blocking in a Case of Paroxysmal Supraventricular Extrasystoles. Wien. Arch. f. inn. Med. **16:** 333, 1929.

In a case of paroxysmal attacks of extrasystoles of supraventricular origin, the authors believe in accordance with Kaufmann's parasystolic theory, that the extrasystoles are due to the rhythmic activity of a center adjoining the sino-auricular node. Under ordinary conditions, the sinus exerts a blocking influence over this secondary center but when the excitability of the ectopic center becomes high enough, the extrasystolic mechanism comes into play. A case is reported with electrocardiographic findings.

Scherf, D., and Zdansky, E.: Influence of Atropine, Adrenalin and Amyl Nitrite on the Size of the Heart. Wien. Arch. f. inn. Med. **16:** 399, 1929.

The authors make use of a device called a roentgenkymograph to study the right and left heart borders in systole and diastole. This apparatus consists of an x-ray film which slides on two lead plates leaving slits which are placed over the heart borders after fluoroscopy.

By means of tracings thus made, they were able to determine that atropine, adrenalin, and amyl nitrite all caused a diminution in the systolic and diastolic diameters, the diminution being in proportion to the increase in pulse rate. The diminution of the heart size with adrenalin is explained by a predominating inotropic action which exceeds the tendency of the increased blood pressure to cause cardiac dilatation.

Redisch, W., and Rosler, H.: Studies of Capillaries in Congenital Heart Disease. Wien. Arch. f. inn. Med. **16:** 463, 1929.

The authors believe that the cyanosis in congenital heart disease is due, not only to the polycythemia and abnormally large amount of reduced hemoglobin but also to the peculiar capillary structure, consisting of numerous arched and winding loops with wide venous limbs. The sluggishness of the capillary stream is a marked feature.

Hurwitz, Samuel H., and Levitin, Joseph: The Value of Phenylhydrazine in the Treatment of Polycythemia Vera. Am. J. M. Sc. **177:** 309, 1929.

The purpose of this report is to record the clinical course of the patient with polycythemia vera treated with phenylhydrazine and to emphasize the value and dangers of this drug as well as the importance of certain criteria for the control of its dosage.

The patient was a woman 42 years old and under observation for two years. Splenomegaly was very slight if present at all. Hematuria was present and had caused her to be treated for Bright's disease. There was a transient palsy of the right arm. This may have been caused by a vascular lesion of the brain due to the formation of a small thrombosis. These patients show a great tendency to venous thrombosis.

Phenylhydrazine hydrochloride produced definite clinical improvement in the patient. The authors concluded that the drug is worthy of being given a trial if the dangers of its use be kept in mind. Guided by frequent counts of the red and white blood corpuscles and by estimations of the serum bilirubin, one may give phenylhydrazine without danger to the patient. It is wise to stop its administration before the red blood count reaches a normal level because its action continues after its withdrawal. The hemolytic crisis observed in these patients may be avoided if additional safeguards be used. Because of the great difference in the response of patients to varying amounts of the drug, quantitative determinations of the serum bilirubin and frequent leucocyte counts should be made. A marked rise in the amount of serum bilirubin means excessive blood destruction, whereas a rising leucocyte count probably indicates great destruction of liver cells.

Finally, it may be stated that the use of phenylhydrazine is no exception to the general observation that the various measures used in the treatment of polycythemia vera are transitory and that the effect produced is purely palliative. General experience seems to show that no matter what therapeutic measure is adopted there is a tendency for the red blood cell count to rise and for the subjective symptoms to return.

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